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(57) Abstract

The present invention relates to novel 3-amino-piperidine derivatives and related compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in treating inflammatory diseases and central nervous system disorders. The compounds are substance P antagonists and are useful in treating diseases mediated by an excess of substance P. The invention also relates to novel intermediates used in the synthesis of such substance P antagonists.

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SUBSTANCE P ANTAGONISTS

Background of the Invention

The present invention relates to novel 3-amino-piperidine derivatives and related compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in treating inflammatory diseases and central nervous system disorders. The compounds are substance P antagonists and are useful in treating diseases mediated by an excess of substance P. The invention also relates to novel intermediates used in the synthesis of such substance P antagonists.

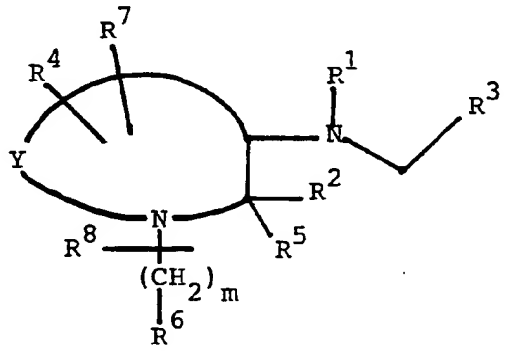
Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine [see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, Vol. 25, p. 1009 (1982)], as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract, like ulcerative colitis and Crohn's disease,

etc. (see D. Regoli in "Trends in Cluster Headache," Edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, 1987, pp. 85-95).

In the recent past, some attempts have been made to provide antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. The few such antagonists thus far described are generally peptide-like in nature and are therefore too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the previously-discussed prior art agents.

Summary of the Invention

The present invention relates to compounds of the formula



I

wherein Y is $(CH_2)_n$ wherein n is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

R^1 is (C_1-C_6) alkyl or hydrogen;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-O-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-O-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-,

di-(C_1-C_6) alkylamino, -NH$\overset{O}{\overset{\|}{C}}$H and -NH$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$ alkyl;

R^5 is hydrogen or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms, wherein one of said carbon atoms, may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl,

pyridyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl,

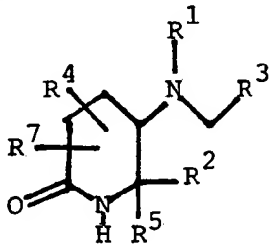
amino, (C_1-C_6) alkylamino, $-NHC(=O)H$ and $-NHC(=O)-(C_1-C_6)$ alkyl; and

R^4, R^6, R^7 and R^8 are each independently selected from hydrogen hydroxy, halo, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-$C(=O)$-, (C_1-C_6)alkyl-O-$C(=O)$-(C_1-C_6)alkyl, (C_1-C_6)alkyl-$C(=O)$-O-, (C_1-C_6)alkyl-$C(=O)$-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-$C(=O)$-, (C_1-C_6)alkyl-$C(=O)$-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^2, with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4, R^6, R^7 nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, and (c) when R^4 and R^7 are attached to the same carbon atom, then either each of R^4 and R^7 is independently selected from hydrogen and (C_1-C_6) alkyl, or R^4 and R^7, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds

of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The present invention also relates to compounds of the formula



I'

wherein R^1, R^2, R^3, R^4 and R^5 are as defined for compounds of the formula I. The compounds of the formula II are novel intermediates used in the synthesis of compounds of the formula I.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched or cyclic moieties or combinations thereof.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

Formulae I and I' above include compounds identical to those depicted but for the fact that one or more hydrogen atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of the substance P receptor in the human brain and in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like. Included among the radiolabelled forms of compounds of the formulae I and II are tritium and C^{14} isotopes thereof.

Preferred compounds of the formula I are those wherein R^1 is hydrogen, R^2 is phenyl, 2-fluorophenyl, 3-fluorophenyl or 3-methoxyphenyl; R^3 is 2-methoxyphenyl; R^4, R^5, R^6 and R^7 are hydrogen; n is 3 or 4 and m is 0.

Specific preferred compounds of the formula I are:

cis-3-(2-chlorobenzylamino)-2-phenylpiperidine;

cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-methylphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methoxyphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methylphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(4-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-thienyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylazacycloheptane;

3-(2-methoxybenzylamino)-4-methyl-2-phenylpiperidine;

3-(2-methoxybenzylamino)-5-methyl-2-phenylpiperidine;

3-(2-methoxybenzylamino)-6-methyl-2-phenylpiperidine;

3-(2-methoxybenzylamino)-2,4-diphenylpiperidine; and

cis-3-(2-methoxybenzylamino)-2-phenylpyrrolidine.

Other compounds of the formula I are:

3-(2-methoxybenzylamino)-5-methylene-2-phenylpiperidine;

5-hydroxy-3-(2-methoxybenzylamino)-2-phenylpiperidine;

4-fluoro-3(2-methoxybenzylamino)-2-phenylpiperidine;

5-hydroxymethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine;

5-fluoromethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine;

3-(2-methoxybenzylamino)-2-phenyl-1,2,3,5-tetrahydropyridine;

6-aza-4-(2-methoxybenzylamino)-5-phenyl-spiro-[2,5]-octane;

5,5-dimethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine;

5,6-dimethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine;

2,5-diphenyl-3-(2-methoxybenzylamino)-2-phenylpiperidine;

4-hydroxy-3-(2-methoxybenzylamino)-4-methyl-2-phenylpiperidine;

2,6-diphenyl-3-(2-methoxybenzylamino)piperidine;

1-(5-cyclohexylpent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

3-(2-methoxybenzylamino)-1-(5-phenylpent-1-yl)-piperidine;

2-benzhydryl-3-(2-methoxybenzylamino)piperidine; and

3-(2-methoxybenzylamino)-4-phenylpiperidine.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, colitis, migraine, psychosis, pain and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in preventing or alleviating such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, colitis, migraine, psychosis, pain and rheumatic diseases such as fibrositis in a mammal, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically

acceptable salt thereof, effective in preventing or alleviating such condition.

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

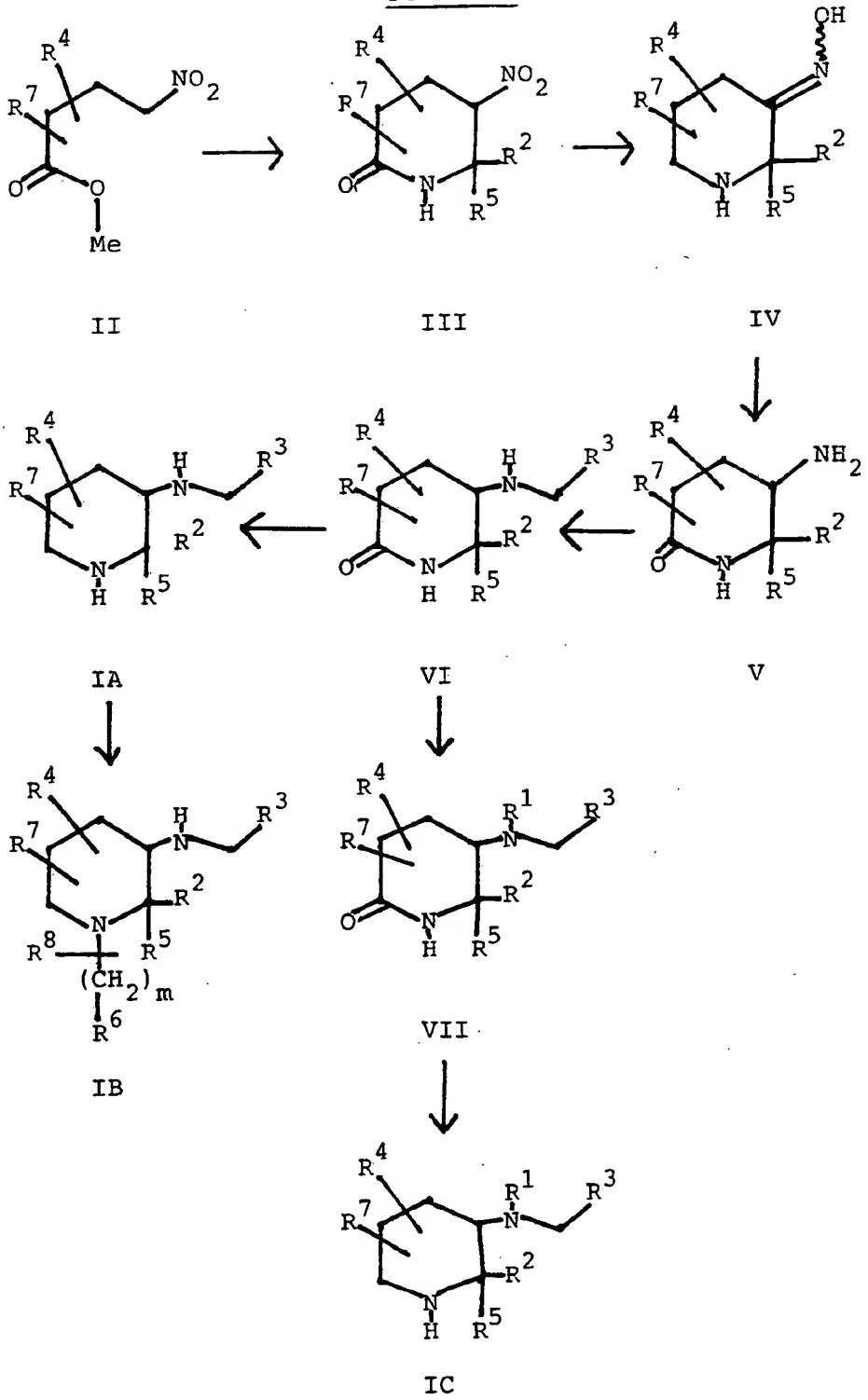
The present invention also relates to a method of treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The compounds of the formula I have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, and mixtures thereof.

Detailed Description of the Invention

The compounds of the formula I may be prepared as described in the following reaction schemes and discussion. Each of the formulas designated IA, IB, IC, and ID represent different classes of compounds having the general formula I. Unless otherwise indicated, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Y, n and m in the reaction schemes and discussion that follow are defined as above.

SCHEME 1



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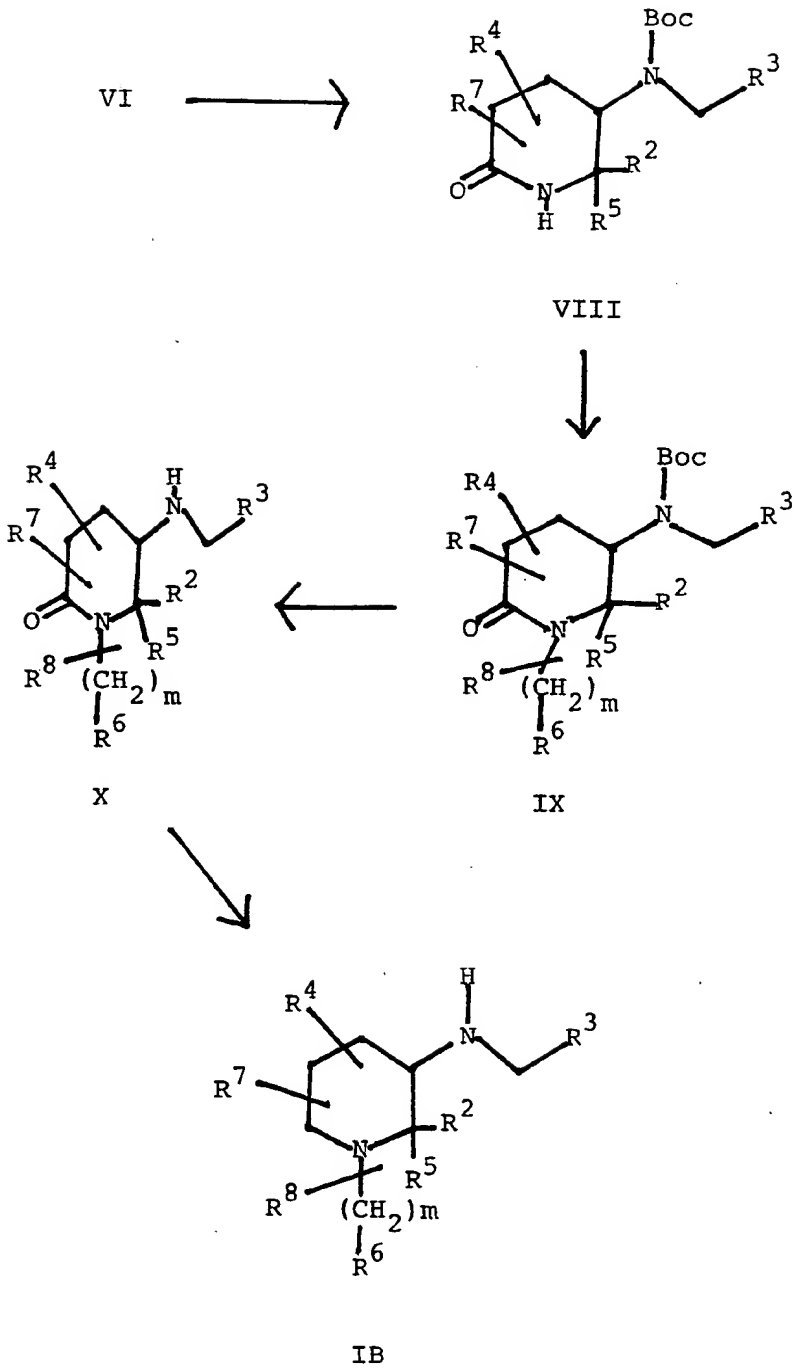

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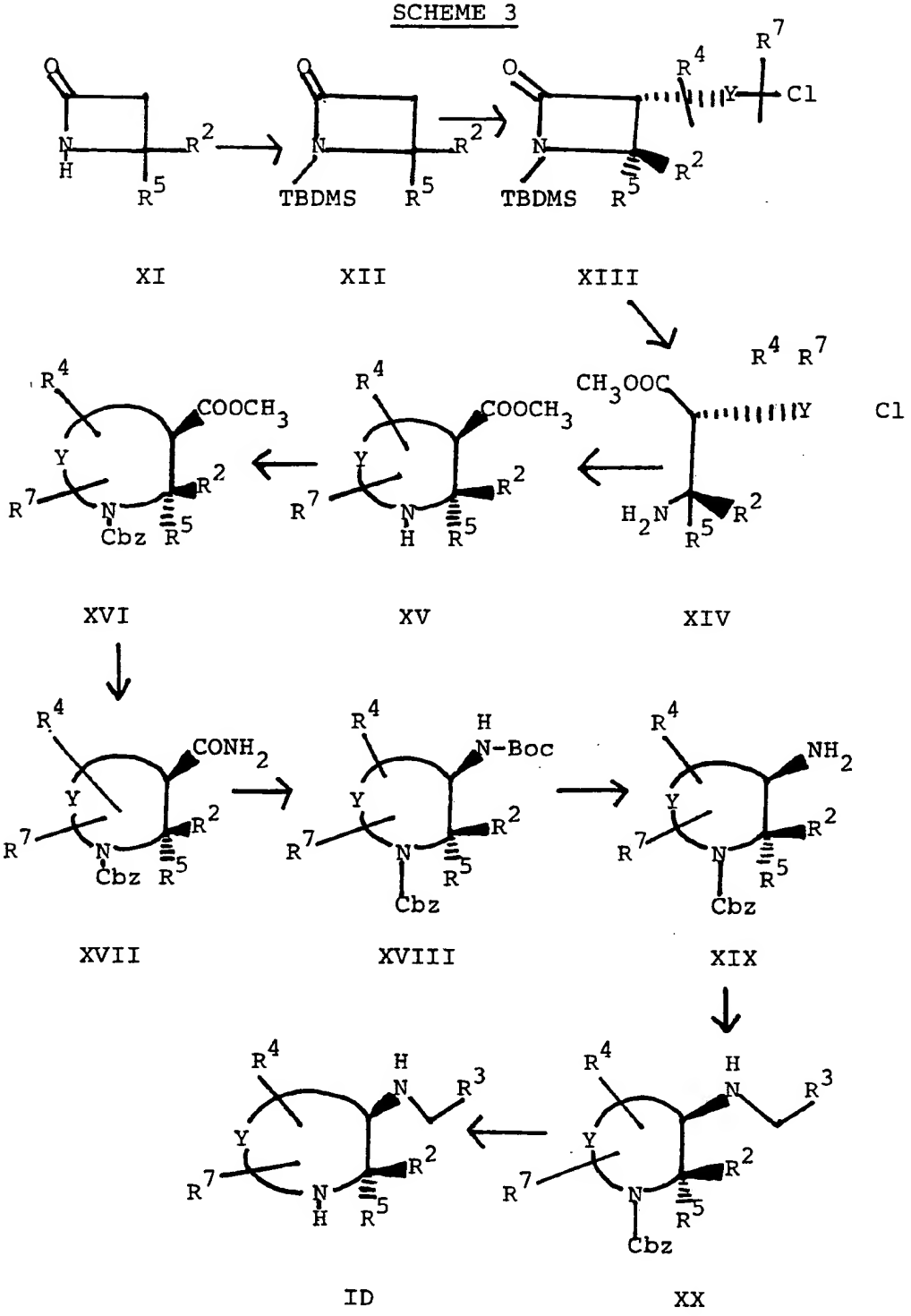
XI
XII
XIII
XIV
XV
XVI
XVII
XVIII
XIX
XX
ID
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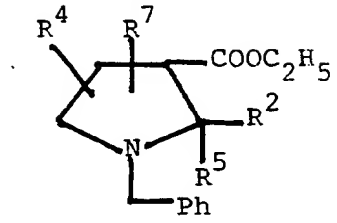
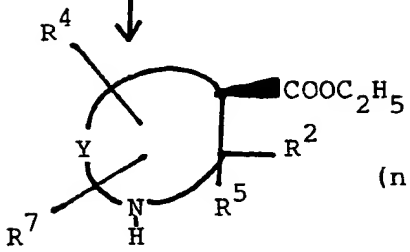
Cl
CONH2
COOCH3
N-Boc
NH2
CH3OOC

SCHEME 4



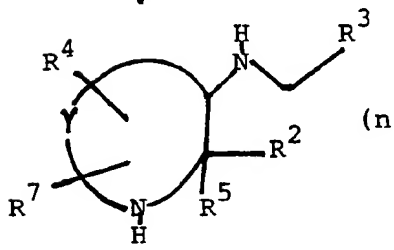
XXI



(n = 2)

XXII

SCHEME 3



(n = 2, racemic)

ID

Scheme 1 illustrates the preparation of compounds of the formulae IA, IB and IC. Formula IA represents compounds of the formula I wherein each of R^1 and R^6 is hydrogen, m is 0 and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring. Formula IB represents compounds of the formula I wherein R^1 is hydrogen and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring. Formula IC represents compounds of the formula I wherein R^6 is hydrogen, m is 0 and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring.

Referring to scheme 1, a compound of the formula II is reacted with a compound of the formula R^5-C(=O)-R^2 in the presence of ammonium acetate, in a polar solvent such as ethanol, acetic acid or dimethyl sulfoxide. Ethanol is the preferred solvent. Temperatures from about room temperature to about 150°C are suitable, with the reflux temperature of the solvent being preferred. This reaction yields, by intramolecular condensation, a compounds of the formula III (Von M. Muhlstadt and B. Schulze, J. Prak. Chem, 317, 919 (1975)).

The condensation product of formula III is then converted, via a Nef reaction, to an oxime of the formula IV. This reaction may be carried out using reagents such as aqueous Ti(III) chloride, potassium permanganate, pyridine/hexamethylphosphoramide complex of molybdenum pentoxide, tributylphosphinediphenyl disulphide or ozone in the presence of a base. Suitable temperatures range from about -100°C to about 0°C. Preferably, the reaction is performed by bubbling ozone through the reaction mixture in the presence of potassium t-butoxide at about

-78°C, and then quenching the reaction mixture with hydroxylamine hydrochloride at ambient temperature.

The oxime of formula IV is then reduced to yield both the cis and trans isomers of a compound of the formula V. Suitable reducing agents include Raney nickel/hydrogen, 10% palladium on charcoal/hydrogen, and aluminum amalgam. Preferably, the reduction is carried out using Raney nickel in ethanol under a hydrogen gas pressure of about 3 atm and at a temperature of about 25°C. Temperatures from about 10 to about 60°C and pressures from about 1 to about 10 atmospheres are also suitable.

Reductive amination of the mixture of cis and trans isomers of the compound of the formula V from the above step with sodium cyanoborohydride and a compound of the formula R^3CHO yields a mixture of the cis and trans isomers of a compound of the formula VI. This reaction is typically carried out in a polar solvent such as acetic acid or a lower alkanol, at a temperature from about 0 to about 50°C. Methanol is the preferred solvent and 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be about 4 to about 5. The cis and trans isomers of the compound of the formula VI so formed can be easily separated by using silica-gel flash chromatography, eluting with 3% methanol in methylene chloride.

Reduction of either the cis or trans isomer of the compound of formula VI, or a mixture thereof, yields a compound of the formula IA having the same stereochemistry. Reducing agents such as lithium aluminum hydride, borane in tetrahydrofuran ("THF") and sodium borohydride-titanium (IV) chloride are suitable; however, best results are obtained by using

borane dimethylsulfide in THF. The reaction may be carried out at temperatures from about room temperature to about 150°C, preferably at the reflux temperature.

The compound of formula IA so formed may be converted to a compound of the formula IB having the same stereochemistry, as illustrated in scheme 1, by reacting it with a compound of the formula $R^6-(CH_2)_n-X$, wherein X is halo, wherein one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond, and wherein one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8. This reaction is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene chloride or dichloroethane, and at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at the reflux temperature in methylene chloride in the presence of triethylamine.

Compounds of the formula IC may be prepared as illustrated in scheme 1 and described below. A compound of the formula VI is reacted with a compound of the formula R^1X, wherein X is halo, to yield a compound of the formula VII having the same stereochemistry (e.g. cis, trans or a mixture thereof). This reaction is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide in a polar solvent such as methylene chloride or dichloroethane, and at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at about the reflux temperature in methylene choride in the presence of triethylamine.

Reduction of the formula VII so formed yields a compound of the formula IC having the same stereochemistry. Reducing agents such as lithium aluminum-hydride, borane in THF and sodium

borohydride-titanium (IV) chloride, or borane dimethylsulfide in THF may be used. Best results are obtained using borane dimethylsulfide in THF. The reaction may be carried out at temperatures from about room temperature to about 150°C, preferably at the reflux temperature.

Scheme 2 illustrates an alternate method of preparing compounds of the formula IB. The starting material for this method is a compound of the formula VI, which is illustrated in scheme 1. In the first step of this method, the basic nitrogen of the starting material is protected with a group such as t-butoxycarbonyl (Boc), trifluoroacetyl, carbobenzyloxy or carboethoxy, by reacting it, respectively, with di-t-butyl dicarbonate trifluoroacetic anhydride, benzyl chloroformate or ethylchloroformate. The preferred protecting group, t-butoxycarbonyl, is illustrated in scheme 2. The reaction of the starting material with di-t-butyl dicarbonate is typically carried out in a polar solvent such as THF, dichloromethane or chloroform, at a temperature from about 0°C to about 100°C. The preferred solvent is dichloromethane and the preferred temperature is room temperature. The reaction is generally carried out for about 0.5 to 72 hours. This reaction yields a compound of the formula VIII having the same stereochemistry as the starting material.

The compound of formula VIII so formed is then reacted with a compound of the formula $X-(CH_2)_m-R^6$ wherein X is halo, or $CH_3SO_2O-(CH_2)_m-R^6$, to form a compound of the formula IX having the same stereochemistry. In each of $X-(CH_2)_m-R^6$ and $CH_3SO_2O-(CH_2)_m-R^6$, one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8 and one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced with a carbon-carbon double bond. This

reaction is generally carried out in the presence of a base such as potassium hydroxide, potassium t-butoxide, lithium diisopropylamine or sodium methoxide, in a polar solvent such as t-butanol or DMF, for about 0.5 to 24 hours. The preferred base is potassium t-butoxide and the preferred solvent is t-butanol. Reaction temperatures will generally range from about -25°C to about 150°C. Generally, the preferred temperature is the reflux temperature of the solvent.

The protecting group is then removed from the compound of formula IX by reacting it with an acid such as hydrochloric acid, trifluoroacetic acid or perchloric acid, to yield a compound of the formula X having the same stereochemistry. The solvent is typically a polar solvent such as methylene chloride, dioxane, ether or THF, preferably dioxane. The reaction is typically run at a temperature from about -10 to about 50°C, preferably about 25°C, for about 0.5 to 24 hours.

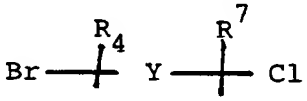
Reduction of the compound of formula X so formed yields a compound of the formula IB having the same stereochemistry. This reaction is carried out in the same manner as described above in the discussion of scheme 1 for preparing compounds of the formula IA from compounds of the formula VI, and for preparing compounds of the formula IC from compounds of the formula VII.

Scheme 3 illustrates a method of preparing compounds of the formula ID. Formula ID represents compounds of the formula I wherein each of R^1 and R^6 are hydrogen, m is 0 and n is 2, 3 or 4. This group of compounds includes those of the formula IA. The method of scheme 3 can be used to prepare the pure 2S,3S enantiomer, the pure 2R,3R enantiomer, or a racemic mixture of a comopund of the formula ID, depending on whether the starting material is, respectively, the R-enantiomer, the S-enantiomer, or a racemic mixture of a compound of the

formula XI. Also, because formula ID includes compounds of the formula IA, the method of scheme 3 can be used to prepare compounds of the formula IA wherein R^4 is attached to the "6" position of the nitrogen containing ring. The method of scheme 3 can also be used to prepare compounds of the formula ID wherein R^2 is benzhydryl.

Referring to scheme 3, compounds of the formula ID are prepared as follows. The pure R-enantiomer, S-enantiomer or a racemic mixture of a compound of the formula XI is reacted with a nitrogen-protecting reagent such as t-butyldimethylsilyl chloride (TBDMS-Cl), t-butyldimethylsilyl triflate (TBDMS-OTf) or benzyl bromide t-butoxide, preferably TBDMS-Cl, to form a compound of the formula XII. The reaction is typically carried out in a polar solvent such as DMF or triethylamine, preferably triethylamine, at a temperature of from about 0 to about 140°C. Room temperature is preferred.

The above reaction is followed by a stereospecific alkylation of the compound of formula XII to form the trans stereoisomer of a compound of the formula XIII. First, the compound of formula XII is reacted with lithium diethylamide in a polar solvent such as ether or THF, preferably THF, at a temperature from about -100°C to about room temperature, preferably about -78°C. Then, a compound of the formula



is added to the reaction mixture to produce the trans isomer of a compound of the formula XIII. Simultaneous removal of the TBDMS group and cleavage of the β-lactam using concentrated sulfuric or perchloric acid, preferably sulfuric acid, in a polar solent such as methanol or ethanol, preferably methanol, yields a compound of the formula XIV. This reaction is typically carried out at a temperature from about room temperature

to about 150°C, preferably at about the reflux temperature of the solvent, for about 0.5 to 16 hours.

The cyclization of the compound of formula XIV to produce a compound of the formula XV is accomplished by heating the crude product of formula XIV from the foregoing reaction at a temperature from about 80 to about 140°C, preferably about 100°C, for about 5 minutes to about 2 days, preferably about 15 minutes, in a high boiling solvent such as DMF or toluene, preferably DMF. Generally, this reaction is conducted in the presence of sodium iodide and sodium bicarbonate. In the compound of formula XV produced by this reaction, R^2 and $-COOCH_3$ are cis to each other.

The compound of formula XV is then treated with benzylchloroformate in a polar solvent such as water, water/acetone, chloroform, dichloroethane or ethyl acetate, in the presence of a base such as triethylamine or sodium bicarbonate, to yield the N-carbobenzyloxy piperidine (N-Cbz piperidine) of formula XVI having the same stereochemistry (i.e. wherein R^2 and $-COOCH_3$ are in the cis configuration). This reaction may be carried out at temperatures from about 0 to about 100°C, preferably about 25°C, for about 5 minutes to 18 hours. Treatment of the compound of formula XVI so formed with about 5 equivalents each of trimethyl aluminum and ammonium chloride in a nonpolar solvent such as benzene or toluene for about 0.5 to 16 hours yields a compound of the formula XVII having the same stereochemisry. Reaction temperatures range from about room temperature to about 100°C, with about 50°C being preferred.

The conversion of the carboxamide group of the compound of formula XVII to form a compound of the formula XVIII having the same stereochemistry may be accomplished by a Hoffmann degradation using reagents such as bromine/sodium methoxide in methanol, lead

tetraacetate in t-butyl alcohol, tin (IV) chloride, iodobenzene bis(trifluoroacetate) in aqueous acetonitrile, sodium bromide or benzyltrimethyl ammonium tribromide. Preferably, the compound of formula XVII is treated with lead tetraacetate in t-butanol. This reaction is typically carried out at a temperature from about room temperature to the reflux temperature of the solvent, preferably the reflux temperature, for about 15 minutes to 10 hours, preferably for about 3 to 5 hours. Reaction of the compound of formula XVIII with a bubbling gaseous acid such as hydrochloric acid, trifluroacetic acid or perchloric acid yields a compound of the formula XIX having the same stereochemistry. The solvent is typically a polar solvent such as methylene chloride, dioxane, ether or THF, preferably dioxane. This reaction is typically carried out at a temperature from about -10 to about 50°C, preferably about 25°C, for about 0.5 to 24 hours.

Reductive amination of the compound of the formula XIX from the above step with sodium cyanoborohydride and a compound of the formula R^3CHO yields a compound of the formula XX having the same stereochemistry. This reaction is generally carried out in a polar solvent such as acetic acid or a lower alkanol, at a temperature from about 0 to about 50°C. Methanol is the preferred solvent and 25°C is the preferred temperature. It is also preferred that the pH of the reaction mixture be about 4 to about 5.

The compound of formula XX is converted into a compound of the formula ID wherein R^2 and the amino group are cis to each other by reacting it with ammonium formate in the presence of palladium on charcoal (e.g. 10% palladium on charcoal). Typically, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room

temperature to about 150°C for about 3 to 24 hours. Preferably, the reaction is conducted in ethanol at room temperature for about .5 to 24 hours.

The trans isomer of a compound of the formula ID (i.e., one wherein the amino group and R^2 are trans to each other) may be prepared by the same procedure described above for obtaining the cis isomer, with the following modification. To prepare the trans isomer, either the compound of formula XV or the compound of formula XVI, after its formation as described above, is treated with potassium t-butoxide or a lithium dialkylamide. The solvent for this reaction is generally a polar solvent such as THF or ether, and the reaction is generally conducted at a temperature from about -78°C to room temperature, preferably at about 0°C, for about 5 minutes to 10 hours.

An alternate method of preparing compounds of the formula ID wherein R^2 is benzhydryl is described in Examples 21-26.

Scheme 4 illustrates a preferred method of preparing compounds of the formula ID wherein n is 2. A compound of the formula XXI is treated with hydrogen gas in the presence of a metal catalyst such a palladium on charcoal, platinum on charcoal or platinum dioxide, preferably palladium on charcoal, and in the presence of an acid such as trifluroacetic acid or hydrochloric acid, to produce a compound of the formula XXII. This reaction is typically carried out in a polar solvent at a pressure of about 3 atm and at a temperature from about 0-60°C, preferably 25°C. The preferred solvent is ethanol. The compound of formula XXII so formed is then converted to a compound of the formula ID by the procedure illustrated in scheme 3 and described above.

Enantiomerically pure compounds of the formula IC (i.e., compounds of the formula ID wherein R^1 is (C_1-C_6)

alkyl rather than hydrogen) may be prepared as follows. A compound of the formula XX, prepared as described above, is alkylated by reacting it with a compound of the formula R^1X, wherein X is halo. This reaction is usually carried out in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene chloride or dichloroethane, and at a temperature from about room temperature to about 200°C. Preferably, the reaction is carried out at the reflux temperature in methylene chloride in the presence of triethylamine. The alkylated product, which has the same stereochemistry as the starting material of formula XX, is then converted to a compound of the formula IC having the same stereochemistry, by reacting it with ammonium formate in the presence of palladium on charcoal (e.g. 10% palladium on charcoal). Typically, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 80°C for about 3 to 24 hours. Preferably, the reaction is conducted in ethanol at room temperature for about 0.5 to 24 hours.

Enantiomerically pure compounds of the formula IB may be prepared by reacting the analogous compound of the formula ID, having the same stereochemistry, with a compound of the formula $R^6-(CH_2)_m-X$, wherein X is halo. In each of $X-(CH_2)_m-R^6$ and $CH_3SO_2O-(CH_2)_m-R^6$, one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8 and one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced with a carbon-carbon double bond. The reaction is performed in the same manner as described above for converting compounds of the formula IA into compounds of the formula IB.

The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the

reactions described above that will be apparent to one skilled in the art.

In each of the reactions discussed or illustrated in schemes 1 to 4 above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

The novel compounds of the formula I and the pharmaceutically acceptable salts thereof are useful as substance P antagonists, i.e., they possess the ability to antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the Formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and thereafter, subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The compounds of Formula I and their pharmaceutically acceptable salts exhibit significant substance P receptor-binding activity and therefore, are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of said substance P activity. Such conditions include gastrointestinal disorders such as ulcers and colitis and other like diseases of the gastrointestinal tract, central nervous system disorders such as anxiety and psychosis, rheumatic diseases such as fibrositis, inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases, respiratory diseases such as asthma, and pain in any of the aforesaid conditions, including migraine. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the formula I and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may

be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very

useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention, as substance P antagonists, is determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin

receptors by means of autoradiography. The substance P antagonist activity of the herein described compounds is evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C. freezer and homogenized in 50 volumes (w./v.) of ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty-minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, 4μg/ml of leupeptin, 2μg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100μl of the test compound made up to a concentration of 1μM, followed by the addition of 100μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800μl of the tissue preparation produced as described above. The final volume is thus 1.0 ml., and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes.

The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC_{50} values are calculated by using standard statistical methods.

The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. This study is carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine

A. 2-Oxo-5-oxamino-6-phenylpiperidine

To a stirred solution of trans -5-nitro-2-oxo-6-phenylpiperidine (27.0 gms, 122.6 mmole) in 1:1 methylene chloride:methanol was added potassium tert. butoxide (135 mmole, 15.1 gms) at 25°C. This reaction mixture was cooled to -78°C and ozone gas was bubbled until (3 hrs) TLC (10% methanol in methylene chloride) indicated no starting material. The reaction mixture was then purged with nitrogen to remove excess ozone, and was then

treated with dimethyl sulfide (60 ml) at -78°C. After warming to room temperature in 30 min., it was treated with an aqueous solution of hydroxylamine (85.2 gms, 1.22 mole) and sodium acetate (50.3 gms, 613 mmole) in water (220 ml). After stirring for 16 hrs, the volatile material was removed using a rotary evaporator. The residue was poured into 1.2 liters of cold water and stirred for 30 min. The precipitated solid was filtered to give 2-oxo-3-oxamino-6-phenylpiperidine (14.0 gms, 56.0%). M.p. 178°C.

^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.04-2.22 (2H, m); 2.4-2.42 (1H, m), 2.71 (1H, dt, J = 8, 16 Hz); 5.02 (1H, d, J = 4 Hz), 7.28-7.41 (5H, m); 8.35 (1H, d, 4 Hz); 10.99 (1H, s).

TLC: (90:10 - methylene chloride:methanol) R_f=0.54.

B. Cis-5-(2-methoxybenzylamino)-2-oxo-6-phenyl-piperidine:

2-Oxo-5-oxamino-6-phenylpiperidine (28.2 gms, 138 mmole) was dissolved (heating on steam bath is necessary to achieve a clear solution) in ethanol (500 ml) containing methanol (50ml). Neutral Raney Ni (80 gms) was added and the mixture was shaken on a Parr shaker under hydrogen (40 psi). After 18 hrs, the reaction mixture was filtered through diatomaceous earth (Celite (Trademark)) which was thoroughly washed with methanol. The organic solvents were removed using a rotary evaporator to afford an oil which solidified on standing (26.2 gms, 100%). ^{1}H-NMR indicated it to be a 3:1 mixture of cis-5-amino-2-oxo-6-phenylpiperidine and trans-5-amino-2-oxo-6-phenylpiperidine, respectively. This mixture was dissolved in methanol (345 ml) and the pH was adjusted to 5 with saturated methanolic hydrochloric acid. Four Å sieves (55 gms), sodium cyanoborohydride (138 mmole) and o-methoxy-benzaldehyde

(22.5 gms, 165 mmole) were added to the system. Stirring was continued (4 hrs) until the reaction was complete as indicated by TLC. The reaction mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate was concentrated using a rotary evaporator. The residue was suspended in water and the pH made basic. The aqueous phase was extracted with methylene chloride (4 x 200 ml) washed with water, brine, and then dried (anhyd. $MgSO_4$) and concentrated to give an oil (47.0 gms) which was flash chromatographed. Elution with 3% methanol in methylene chloride afforded a white solid (19.6 gms).

^1H NMR ($CDCl_3$) δ 1.81-1.96 (1H, m); 2.0-2.18 (1H, m); 2.4 (1H, dt, J = 4.5, 16 Hz); 2.75 (1H, ddd, J = 6.5, 10.5 16 Hz); 3.48 (3H, s); 3.54 (1H, dd, J = 13.8 Hz); 3.76 (1H, dd, J = 13.8 Hz); 4.72 (1H, d, J = 4Hz); 5.72 (1H, bs); 6.71 (1H, d, J = 8 Hz); 6.8 (1H, t, J = 6.8 Hz); 7.04 (1H, dd, J = 1.8, 7.2 Hz); 7.17 (1H, dt, J = 1.6, 8.2 Hz); 7.2-7.44 (5H, m).

HRMS: Calculated for $C_{19}H_{22}N_2O_2$: 310.1682;
Found 310.1649.

TLC: (90:10 - methylene chloride:methanol) R_f = 0.47.

C. Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine

Borane dimethylsulfide in tetrahydrofuran (2M, 158 ml, 315 mmole) was added to a solution of cis - 5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine (19.6 g, 63.0 mmole) in tetrahydrofuran (500 ml) under nitrogen and the reaction mixture was heated at reflux for 18 hrs. At the end of this period, the reaction mixture was cooled and the excess borane dimethylsulfide was cautiously decomposed by dropwise addition of methanol. The contents of the reaction mixture were then concentrated under vacuum. Ethanol (500 ml) and powdered

potassium carbonate (17.5 g, 126 mmole) were added to the residue and the reaction mixture was heated at reflux (18 hrs). Then the reaction mixture was concentrated under vacuum and the residue was extracted with methylene chloride (4 x 250ml) and dried (anhydrous $MgSO_4$). The organic solvents were removed under vacuum to afford a residue which was dissolved in a minimum amount of methylene chloride. To this solution was added excess hydrochloric acid/ether, thus precipitating the dihydrochloride salt of cis-3-(2-methoxybenzylamino)-2-phenylpiperidine, which was isolated by filtration. This was heated at reflux in chloroform (400ml) for 3 hours and filtered to give the essentially pure hydrochloride salt of the title compound (22.4 gms, m.p. 245°C, 96%), which was crystallized from a mixture of hot methanol-ethanol to afford a white crystalline solid (19.2 gms, 83%).

M.p. 255° (HCl salt). ^{1}H-NMR ($CDCl_3$, free base) δ 7.1-7.3 (6H, m); 6.97 (1H, dd, J = 1.7, 7.4 Hz); 6.79 (1H, bt, J = 7.4 Hz); 6.66 (1H, d, J = 8.2 Hz); 3.87 (1H, d, J = 2.3 Hz); 3.67 (1H, d, J = 11.4 Hz): 3.44 (3H, s); 3.4 (1H, d, J = 14 Hz); 3.22-3.3 (1H, bd, J = 12.2 Hz); 2.72-2.86 (2H, m); 2.09-2.19 (1H, bd, J = 13.7 Hz); 1.84-2.01 (1H, dt, J = 4.0, 13.0 Hz); 1.53-1.7 (1H, dt, J = 3.5, 13.4 Hz); 1.33-1.45 (1H, bd, J = 12.5 Hz). ^{13}C-NMR ($CDCl_3$, free base) δ 157.6, 142.5, 129.6, 128.3, 128.2, 127.8, 126.5, 126.3, 120.0, 109.8, 64.0, 54.8, 54.7, 47.8, 46.7, 28.2, 20.4. HRMS Calcd. for $C_{19}H_{24}N_2O$: 296.1886. Found: 296.1904.

TLC : (90:10 - methylene chloride:methanol) R_f = 0.39.

EXAMPLE 2

Cis-1-allyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

Under a nitrogen atmosphere, in a round-bottom flask, were placed 60 mg (0.2 mmol) of the title compound

of Example 1 and 0.2 ml of CH_2Cl_2. To this system were added 28μl (0.2 mmol) of triethylamine and 17.5μl (0.2 mmol) of allyl bromide, and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate, the layers were separated, and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated with a rotary evaporator. The crude material was purified by flash column chromatography to obtain 26 mg of the title compound.

^1H NMR ($CDCl_3$) δ 7.20 (m, 5H), 7.03 (t, 1H, J = 6 Hz), 6.79 (d, 1H, J = 6 Hz), 6.88 (t, 1H, J = 6 Hz), 6.57 (d, 1H, J = 6 Hz), 5.78 (m, 1H), 4.94 (m, 2H), 3.62 (d, 1H, J = 12 Hz), 3.40 (s, 3H), 3.32 (d, 1H, J = 12 Hz), 3.26 (d, 1H, J = 2 Hz), 3.18 (m, 1H), 2.56 (m, 1H), 2.36 (m, 1H), 1.98 (m, 3H), 1.68 (m, 1H), 1.38 (m, 2H).
HRMS: Calcd for $C_{22}H_{28}N_2O$: 336.2202. Found: 336.2216.

EXAMPLE 3

Cis-1-ethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

A. Cis-5-(N-tert-butoxycarbonyl-2-methoxybenzylamino)-2-oxo-6-phenylpiperidine

Under a nitrogen atmosphere in a round-bottom flask were placed 2.0 g (6.4 mmol) of cis-5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine, 7 mL of CH_2Cl_2 and 14.1 g (64.5 mmol) of di-tert-butyldicarbonate. The reaction mixture was stirred at room temperature for 4 days, poured into saturated aqueous sodium bicarbonate and extracted with two portions of CH_2Cl_2. The combined organic fractions were washed with H_2O, dried (Na_2SO_4) and concentrated with a rotary evaporator to obtain 16 g of oil. The crude material was purified by flash column chromatography to obtain 2.4 g (91% yield) of cis-5-(N-

tert-butoxycarbonyl-2-methoxybenzylamino)-2-oxo-6-phenylpiperidine as a white solid.

^{1}H NMR ($CDCl_3$) 7.34 (m, 3H), 7.14 (m, 2H), 7.04 (m, 1H), 6.92 (d, 1H, J = 7 Hz), 6.79 (t, 1H, J = 7 Hz), 6.62 (d, 1H, J = 7 Hz), 5.00, 4.86 (2m, 1H), 4.68, 4.46 (2m, 1H), 4.00, 3.78 (2d, 1H, J = 18 Hz), 3.58 (s, 3H), 2.82 (d, 1H, J = 18 Hz), 2.20 (m, 2H), 1.80 (m, 1H), 1.44 (m, 1H), 1.53, 1.36 (2s, 3H).

B. Cis-N-ethyl-5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine

Under a nitrogen atmosphere in a round-bottom flask were placed 50 mg (0.12 mmol) of cis-5-(N-tert-butoxycarbonyl-2-methoxybenzylamino)-2-oxo-6-phenylpiperidine and 0.2 mL of THF. To the system were added 13.5 mg (0.12 mmol) of potassium tert-butoxide and 20 L (0.24 mmol) of ethyl iodide. The reaction mixture was stirred at room temperature for 3 hours (during this period, additional potassium tert-butoxide (13.5 mg) and ethyl iodide (20 L) were added to the system). The mixture was partitioned between CH_2Cl_2 and aqueous sodium bicarbonate, the layers were separated and the aqueous phase was extracted with three portions of CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated with a rotary evaporator. The crude material was purified by flash column chromatography using 3:97 methanol/chloroform as the eluant to obtain 42 mg of cis-N-ethyl-5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine.

^{1}H NMR ($CDCl_3$) δ 7.36 (m, 3H), 7.10 (m, 3H), 6.92 (d, 1H, J = 6Hz), 6.80 (t, 1H, J = 6 Hz), 6.63 (d, 1H, J = Hz), 4.97, 4.82 (2m, 1H), 4.60, 4.40 (2m, 1H), 4.00 (m, 1H), 3.80 (m, 1H, J = 18 Hz), 3.58 (s, 3H), 2.80 (d, 1H, J = 18 Hz), 2.50 (m, 3H), 1.80 (m, 1H), 1.56, 1.38 (2s, 9H), 1.06 (t, 3H, J = 7Hz). Mass spectrum m/e 438 (parent).

C. Cis-1-ethyl-3-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine.

In a round bottom flask were placed 173 mg (0.39 mmol) of cis-N-ethyl-5-(N-tert-butoxycarbonyl-2-methoxybenzylamino)-2-oxo-6-phenylpiperidine and 0.5 mL of dioxane. To this system were added 5 mL of dioxane saturated with HCl. The reaction mixture was stirred at room temperature for 2.5 hours and concentrated with a rotary evaporator. The residue was partitioned between saturated aqueous sodium bicarbonate and chloroform and extracted with three portions of chloroform.

The combined organic fractions were dried (Na_2SO_4) and concentrated to obtain 84 mg of cis-1-ethyl-3-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine, which was used immediately without further purifiction; ^1H NMR ($CDCl_3$) δ 7.28 (m, 7H), 6.90 (t, 1H, J = 6 Hz), 6.81 (d, 1H, J = 6 Hz), 4.68 (d, 1H, J = 2 Hz), 3.88 (m, 3H), 3.74 (s, 3H), 3.14 (m, 1H), 2.56 (m, 3H), 1.76 (m, 1H), 1.54 (m, 1H), 1.04 (t, 3H, J = 6 Hz).

D. Cis-1-Ethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

Under a nitrogen atmosphere, in a round-bottom flask were placed 80 mg (0.24 mmol) of the amine prepared above and 5 mL of THF. To this system was added 0.59 mL (1.18 mmol) of 2.0 M borane methylsulfide in THF, and the reaction mixture was heated overnight at 60°C. The mixture was cooled, ca. 2 mL of methanol was added carefully to the system, and the mixture was stirred for 1 hour and concentrated with a rotary evaporator. Sixty-six mg (0.48 mmol) of K_2CO_3 in 2 mL of ethanol was added to the system, and the mixture was heated at reflux for 2.5 hours, cooled and concentrated. The residue was partitioned between H_2O and CH_2Cl_2, the layers were separated and the aqueous phase was extracted with three

portions of dichloromethane. The combined organic fractions were dried (Na_2SO_4) and concentrated to obtain 64 mg of a yellow oil. This oil was dissolved in CH_2Cl_2, and then ether saturated with HCl was added to the solution. The resulting yellow solid was collected, affording 60 mg of the hydrochloride salt of the title compound.

^1H NMR (free base, $CDCl_3$) δ 7.22 (m, 5H), 7.03 (t, 1H, J = 6 Hz), 6.78 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 6 Hz), 6.56 (d, 1H, J = 6 Hz), 3.62 (d, 1H, J = 12 Hz), 3.39 (s, 3H), 3.31 (d, 1H, J = 12 Hz), 3.25 (d, 1H, J = 2Hz), 3.16 (m, 1H), 2.55 (m, 2H), 1.99 (m, 2H), 1.86 (m, 2H), 1.40 (m, 2H), 0.90 (t, 3H, J = 6 Hz). HRMS Calc'd. for $C_{21}H_{28}N_2O$: 324.2201. Found: 324.2193.

The title compounds of Examples 4-14 were prepared by a procedure similar to that described in Example 2.

EXAMPLE 4

Cis-3-(2-methoxybenzylamino)-2-phenyl-1-(prop-1-yl)piperidine

M.p. 223-225°C. ^1H NMR ($CDCl_3$) δ 7.28 (m, 5H), 7.10 (t, 1H, J = 6 Hz), 6.87 (d, 1H, J = 6 Hz), 6.74 (t, 1H, J = 6 Hz), 6.60 (d, 1H, J = 6 Hz), 3.86 (d, 1 H, J = 12 Hz), 3.46 (d, 1H, J = 12 Hz), 3.40 (s, 3H), 3.29 (m, 1H), 2.64 (m, 1H), 2.50 (m, 1H), 2.02 (m, 4H), 1.46 (m, 4H), 0.72 (t, 3H, J = 7 Hz). Mass spectrum m/e 338 (parent).

EXAMPLE 5

Cis-1-butyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

M.p. 139-140°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.20 (m, 5H), 7.02 (t, 1H, J = 6 Hz), 6.77 (d, 1 H, J = 6 Hz), 6.66 (t, 1H, J = 6 Hz), 6.55 (d, 1H, J = 6 Hz), 3.60 (d, 1H, J = 14 Hz), 3.37 (s, 1H), 3.30 (d, 1H, J = 14 Hz), 3.22 (d, 1H, J = 2Hz), 3.16 (m, 1H), 2.48 (m, 2H), 1.98

(m, 3H), 1.36 (m, 3H), 1.08 (m, 3H), 0.71 (t, 3H, J = 9 Hz). Mass spectrum m/e 352 (parent).

EXAMPLE 6

Cis-3-(2-methoxybenzylamino)-2-phenyl-1-(2-phenyleth-1-yl)piperidine

^{1}H NMR ($CDCl_3$) δ 7.18 (m, 10H), 6.92 (d, 1H, J = 6 Hz), 6.82 (d, 1H, J = 6 Hz), 6.71 (t, 1H, J = 6Hz), 6.00 (d, 1H, J = 6 Hz), 3.66 (d, 1H, J = 15 Hz), 3.44 (s, 3H), 3.35 (m, 2H), 2.72 (m, 3H), 2.60 (m, 1H), 2.12 (m, 4H), 1.68 (m, 1H), 1.44 (m, 2H). HRMS Calc'd. for $C_{27}H_{32}N_2O$: 400.2515. Found: 400.2521.

EXAMPLE 7

Cis-3-(2-methoxybenzylamino)-2-phenyl-1-propargylpiperdine

M.p. 147-149°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 5H), 7.02 (t, 1H, J = 7 Hz), 6.82 (d, 1H, J = 7Hz), 6.68 (t, 1H, J = 7 Hz), 6.56 (d, 1H, J = 7 Hz), 3.62 (d, 1H, J = 12 Hz), 3.47 (d, 1H, J = 2Hz), 3.38 (m, 4H), 3.30 (d, 1H, J = 12 (Hz), 3.21 (d, 1H, J = 2 Hz), 3.15 (d, 1H, J = 2 Hz), 2.94 (m, 1 H), 2.55 (m, 2H), 2.06 (m, 3H), 1.40 (m, 1H). Mass spectrum m/e 334 (parent). Calc'd. for $C_{22}H_{26}OH_2$ 2HCl·2.75 H_2O: C, 57.83; H, 7.39; N, 6.13. Found: C, 57.81; H, 7.58; N, 5.91.

EXAMPLE 8

Cis-3-(2-Methoxybenzylamino)-2-phenyl-1-(3-phenylprop-1-yl)piperidine

M.p. 120-125°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 1H), 6.80 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 6Hz), 6.58 (d, 1H, J = 8 Hz), 3.62 (d, 1H, J = 14 Hz), 3.40 (s, 3H), 3.32 (d, 1H, J = 14 Hz), 3.26 (d, 1H, J = 2 Hz), 3.18 (m, 1H), 2.52 (m, 2H), 2.35 (m, 1H), 2.00 (m, 3H), 1.76 (m, 4H), 1.42 (m, 2H). Mass spectrum m/e 414 (parent). Calc'd. for $C_{28}H_{34}ON_2$ 2HCl·2.75H_2O: C, 62.62; H, 7.79; N, 5.22. Found: C, 62.63; H, 7.82; N, 5.08.

EXAMPLE 9

Cis-1-(carboxamidomethyl)-3-(2-methoxybenzylamino)-2-phenylpiperidine

M.p. 235°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), 7.05 (t, 1H, J = 7 Hz), 6.82 (d, 1H, J = 7 Hz), 6.68 (t, 1H, J = 7 Hz), 6.56 (d, 1H, J = 7 Hz), 3.64 (d, 1H, J = 16 Hz), 3.39 (d, 1H, J = 2 Hz), 3.30 (s, 3H), 3.29 (d, 1H, J = 16 Hz), 3.20 (d, 1H, J = 18 Hz), 3.06 (m, 1H), 2.57 (m, 1H), 2.36 (d, 1H, J = 18 Hz), 2.06 (m, 3H), 1.41 (m, 2H). Mass spectrum m/e 353 (parent).

EXAMPLE 10

Cis-1-Carboxymethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

M.p. 58°C (HCl salt, very hygroscopic). ^{1}H NMR (CD_3OD) δ 7.72 (m, 2H), 7.62 (m, 3H), 7.36 (t, 1H, J = 7 Hz), 7.28 (d, 1H, J = 7 Hz), 6.96 (m, 2H), 5.14 (m, 1H), 4.18 (m, 2H), 4.00 (m, 1H), 3.66 (m, 3H), 3.40 (m, 1H), 2.34 (m, 5H), 2.07 (m, 1H). Mass spectrum m/e 354 (parent).

EXAMPLE 11

Cis-3-(2-Methoxybenzylamino)-2-phenyl-1-(5-phenylpent-1-yl)piperidine

M.p. 109°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 11H), 6.78 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 6 Hz), 6.56 (d, 1H, J = 6 Hz), 3.62 (d, 1H, J = 14 Hz), 3.40 (s, 3H), 3.32 (d, 1H, J = 14 Hz), 3.24 (d, 1H, J = 2 Hz), 3.16 (m, 1H), 2.50 (m, 4H), 2.00 (m, 4H), 1.76 (m, 1H), 1.42 (m, 5H), 1.14 (m, 2H). Mass spectrum m/e 442 (parent).

EXAMPLE 12

Cis(2-Methoxybenzylamino)-2-phenyl-1-(4-phenylbut-1-yl)piperidine

M.p. 65-70°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 11H), 6.84 (d, 1H, J = 7 Hz), 6.73 (t, 1H, J = 7 Hz), 6.62 (d, 1H, J = 7 Hz), 3.68 (d, 1H, J = 12 Hz), 3.44 (s,

3H), 3.38 (d, 1H, J = 12 Hz), 3.30 (d, 1H, J = 3 Hz), 3.18 (m, 1H), 2.34 (m, 4H), 2.02 (m, 3H), 1.80 (m, 1H), 1.47 (m, 6H). Mass spectrum m/e 428 (parent).

EXAMPLE 13

Cis-3-(2-Methoxybenzylamino)-2-phenyl-1-(3-phenyl-prop-2-ene-1-yl)piperidine

M.p. 54-58°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 11H), 6.84 (d, 1H, J = 6 Hz), 6.72 (t, 1H, J = 6 Hz), 6.60 (d, 1H, J = 6 Hz), 6.28 (m, 2H), 3.76 (d, 1H, J = 12 Hz), 3.40 (m, 5H), 3.20 (m, 1H), 2.56 (m, 2H), 2.04 (m, 4H), 1.44 (m, 1H). Mass spectrum m/e 412 (parent).

EXAMPLE 14

Cis-3-(2-Methoxybenzylamino)-1-(2-phenoxyeth-1-yl)-2-phenylpiperidine

^{1}H NMR ($CDCl_3$) δ 7.26 (m, 7H), 7.08 (t, 1H, J = 6 Hz), 6.80 (m, 5H), 6.61 (d, 1H, J = 6 Hz), 4.04 (m, 1H), 3.68 (d, 1H, J = 14 Hz), 3.42 (s, 3H), 3.37 (d, 1H, J = 14 Hz), 2.97 (m, 1H), 2.60 (m, 1H), 2.28 (m, 2H), 2.06 (m, 3H), 1.47 (m, 1H), 1.26 (m, 3H). Mass spectrum m/e 323 (parent).

The title compounds of Examples 15-17 were prepared by a procedure similar to that described in Example 3.

EXAMPLE 15

Cis-3-(2-Methoxybenzylamino)-1-methyl-2-phenylpiperidine

M.P. 58°C (HCl salt, very hygroscopic, dec). ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 5H), 7.04 (t, 1H, J = 6 Hz), 6.82 (d, 1H, J = 6 Hz), 6.78 (t, 1H, J = 6 Hz), 6.58 (d, 1H, J = 6 Hz), 3.62 (d, 1H, J = 12 Hz), 3.42 (s, 3H), 3.32 (d, 1H, J = 12 Hz), 3.02 (m, 2H), 2.56 (m, 1H), 2.04 (m, 3H), 2.02 (s, 3H), 2.38 (m, 2H). Mass spectrum m/e 310 (parent).

EXAMPLE 16

Cis-1-Benzyl-3-(2-Methoxybenzylamino)-2-phenylpiperidine

M.p. 68-70°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 11H), 6.83 (d, 1H, J = 6 Hz), 6.70 (t, 1H, J = 6 Hz), 6.61 (d, 1H, J = 6 Hz), 3.85 (d, 1H, J = 14 Hz), 3.64 (d, 1H, J = 14 Hz), 3.47 (s, 3H), 3.35 (m, 2H), 2.96 (m, 1H), 2.79 (d, 1H, J = 14 Hz), 2.62 (m, 1H), 1.96 (m, 3H), 1.38 (m, 2H). Mass spectrum m/e 386 (parent).

EXAMPLE 17

Cis-1-(2-Hydroxyeth-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine

M.p. 148-149°C (HCl salt, dec). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 7.12 (t, 1H, J = 7 Hz), 6.88 (d, 1H, J = 7 Hz), 6.75 (t, 1H, J = 7 Hz), 6.63 (d, 1H, J = 7 Hz), 3.70 (m, 3H), 3.44 (m, 5H), 3.26 (m, 1H), 2.85 (m, 1H), 2.64 (m, 1H), 2.06 (m, 3H), 1.88 (m, 1H), 1.30 (m, 2H). HRMS Calc'd. for $C_{21}H_{28}N_2O_3$: 340.2150. Found: 340.2142. Calc'd. for $C_{21}H_{28}O_2N_2$ $2HCl \cdot 2.6H_2O$: C, 54.81; H, 7.71; N, 6.08. Found; C, 54.81; H, 8.02; N, 5.82.

EXAMPLE 18

Cis-3-(2-Methoxybenzylamino)-2-phenylpyrrolidine

1-Benzyl-3-carboethoxy-2-phenyl-2,3-didehydropyrrolidine, made according to the procedure described by Celerier et al., Tetrahedron Lett., 28, 6597 (1987), (2.0 g, 6.5 mmol) was dissolved in 70 mL of ethanol. To this solution was added 1 mL of concentrated aqueous HCl and 2.0 g of 5% palladium on carbon. The mixture was placed on a Parr apparatus (40 p.s.i. H_2) for 1 hour. The mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate was concentrated with a rotary evaporator. Saturated aqueous sodium bicarbonate was added to the residue until the liquid was basic (pH 8), and the material was extracted with three portions of CH_2Cl_2. The combined organic fractions were

dried (Na_2SO_4) and concentrated (rotary evaporator) to obtain 1.1 g of an oil. This material was suspended in 10 mL of 10% aqueous sodium bicarbonate, and the system was cooled in an ice bath. To the system was added 0.65 mL (4.6 mmol) of benzylchloroformate, the cold bath was removed and the mixture was stirred for 30 min. Ether was then added, the layers were separated, and the ether phase was washed with water, dried (Na_2SO_4) and concentrated with a rotary evaporator. The crude material was purified by flash column chromatogrpahy (80 g of silica gel) using 1:3 ethyl acetate/hexanes as the eluant to obtain 940 mg of pure 1-benzyl-3-carboethoxy-2-phenylpyrrolidine. ^1H NMR ($CDCl_3$) 7.16 (m, 9H), 6.76 (m, 1H), 5.02 (m, 3H), 3.78 (m, 3H), 3.54 (m, 1H), 3.34 (m, 1H), 2.40 (m, 1H), 2.02 (m, 1H), 1.94 (t, 3H, J = 6 Hz). Mass spectrum m/e 353 (parent).

This material was converted to the title compound by a procedure similar to that described in Example 63 E-G. ^1H NMR ($CDCl_3$) δ 7.26 (m, 5H), 7.12 (t, 1H, J = 7 Hz), 6.98 (d, 1H, J = 7 Hz), 6.80 (t, 1H, J = 7 Hz), 6.70 (d, 1H, J = 6 Hz), 4.11 (d, 1H, J = 4 Hz), 3.86 (d, 1H, J = 12 Hz), 3.52 (s, 3H), 3.42 (d, 1H, J = 12 Hz), 3.34 (m, 1H), 3.25 (m, 1H), 2.98 (m, 1H), 1.9 (m, 2H).

EXAMPLE 19

Cis-3-(N,N-Methyl-2-methoxybenzyl-amino)-2-phenylpiperidine

Under a nitrogen atmosphere in a round-bottom flask were placed 75 mg (0.24 mmol) of the lactam 5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine, 0.036 mL (0.48 mmol) of methyl iodide, 0.066 mL (0.48 mmol) of triethylamine and 0.2 mL of THF. The reaction mixture was stirred at room temperature for 5 hours and poured into saturated aqueous sodium bicarbonate. This mixture was extracted with three portions of CH_2Cl_2. The CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated with a

rotary evaporator. The residue was resubjected to the above conditions, employing the following quantities of reagents: 0.11 mL (1.4 mmol) of methyl iodide and 0.066 mL (0.48 mmol) of triethylamine. The mixture was stirred at room temperature for 7.5 hours, and during this period additional methyl iodide (0.11 mL) was added to the system. The reaction mixture was treated as described above to obtain 70 mg of a clear colorless oil. The crude material was purified by flash column chromatography (7 g of silica gel) using 3:97 methanol/chlorform as the eluant to obtain 44 mg of cis-3-(N,N-methyl-(2-methoxybenzylamino)-2-phenylpiperidin-6-one.

^{1}H NMR ($CDCl_3$) δ 1.86 (m, 5H), 2.52 (m, 1H), 2.70 (m, 1H), 3.34 (m, 1H), 3.52 (d, 1H, J = 14), 3.74 (d, 1H, J = 14), 3.84 (s, 3H), 4.68 (m, 1H), 6.90, (m, 2H), 7.80 (m, 7H), HRMS: Calcd. for $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1884.

Under a nitrogen atmosphere in a round-bottom flask were placed 54 mg (0.17 mmol) of cis-3-(N,N-methyl-(2-methoxy)benzylamino)-2-phenylpiperidin-6-one and 2.5 mL of THF. To the system was added slowly 0.43 mL (0.86 mmol) of 2.0 M borane-methylsulfide complex in THF, and the reaction mixture was heated at 60°C overnight. The reaction mixture was cooled to room temperature, methanol was added slowly to the system and the mixture was stirred at room temperature for 30 min and concentrated with a rotary evaporator. Two milliliters of ethanol and 48 mg (0.35 mmol) of potassium carbonate were then added, and the reaction mixture was heated at reflux for 4 hours and cooled to room temprature. The solvent was removed with a rotary evaporator. The residue was partitioned between chloroform and water, the layers were separated, and the aqueous phase was extracted with chloroform. The combined organic fractions were dried (Na_2SO_4) and

concentrated to obtain 75 mg of an oil. This oil was dissolved in a minimum volume of CH_2Cl_2, and ether saturated with HCl was added to the solution. Water was added to the system, and the mixture was washed with two portions of CH_2Cl_2. The aqueous phase was basified with aqueous sodium hydroxide and extracted with four portions of CH_2Cl_2. These combined fractions were dried and concentrated to obtain 20 mg of the title compound as an oil.

^1H NMR ($CDCl_3$) δ 7.62 (d, 2H, J = 6 Hz), 7.22 (m, H), 7.06 (t, 1H, J = 7 Hz), 6.82 (d, 1H, J = 6 Hz), 6.70 (m, 2H), 4.06 (d, 1H, J = 2 Hz), 3.71 (s, 3H), 3.62 (d, 1H, J = 12 Hz), 3.44 (d, 1H, J = 12 Hz), 3.11 (m, 1H), 2.81 (m, 2H), 2.19 (s, 3H), 1.73 (m, 4H). Mass spectrum m/e 310 (parent).

EXAMPLE 20

Cis-2,4-Diphenyl-3-(2-methoxybenzylamino)piperidine

Under a nitrogen atmosphere in a round-bottom flask equipped with a reflux condenser were placed 21.1 g (89 mmol) of ethyl 4-nitro-3-phenylbutyrate (McMurray, J.E. et. al., Syn.Comm., 8, 53(1978)) and 90 mL of ethanol. To the system was added 9.04 mL (89 mmol) of benzaldehyde and 13.7 g (180 mmol) of ammonium acetate, and the reaction mixture was heated at 70°C overnight. The reaction mixture was cooled, a small volume of ethanol was added and the suspension was filtered. The collected solid was rinsed with a small volume of ethanol followed by ether to afford 22.7 g of 4,6-diphenyl-5-nitro-2-oxopiperidine.

^1H NMR (DMSO) δ 2.53 (dd, 1H, J = 6, 18), 2.82 (m, 1H), 3.88 (m, 1H), 4.80 (d, 1H, J = 8), 5.47 (t, 1H, J = 8), 7.3 (m, 10H). Mass spectrum m/e 296 (parent).

In a round-bottom flask were placed 15 g (50.6 mmol) of the nitro lactam 4,6-diphenyl-5-nitro-2-oxopiperidine and 85 mL of CH_2Cl_2. Potassium tert-butoxide (5.72 g,

50.6 mmol) was added and the mixture was stirred for 15 min. To this system was added 85 mL of methanol. The mixture was stirred for 15 min and the system was cooled to -78°C. Ozone was bubbled thorugh the reaction mixture for 4 hours, nitrogen was bubbled through the mixture, 10 mL of dimethyl sulfide was added and nitrogen was bubbled through the mixture overnight. A mixture of water and CH_2Cl_2 was added to the system and the resulting solid (8.8 g of a mixture of the nitro lactam 4,6-diphenyl-5-nitro-2-oxopiperidine and 2,5-dioxo-4,6-diphenyl-piperidine was collected by suction filtration. The filtrate was concentrated with a rotary evaporator and the residue was partitioned between CH_2Cl_2 and water. The layers were separated, and the aqueous phase was extracted with two portions of CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated to afford 5.14 g of crude 2,5-dioxo-4,6-diphenylpiperidine which was used immediately without further purification.

Under a nitrogen atmosphere in a round-bottom flask were placed 2,5-dioxo-4,6-diphenylpiperidine (5.14 g, 19 mmol) and 75 mL of ethanol. A solution of 3.96 g (57 mmol) of hydroxylamine hydrocloride and 7.74 g (95 mmol) of sodium acetate in 25 mL of water were added and the reaction mixture was stirred at room temperature. The reaction mixture was concentrated to ca. 1/2 its initial volume, and the resulting precipitate was collected by suction filtration. This precipitate (1.5 g) was washed with saturated aqueous sodium bicarbonate, water and ether to afford 722 mg of 4,6-diphenyl-5-oxamino-2-oxopiperidine as a white solid. ^1H NMR (DMSO) δ 2.52 (m, 2H), 2.76 (m, 1H), 4.12 (m, 1H), 5.80 (m, 1H), 7.30 (m, 10H), 8.24 (m, 1H). Mass spectrum m/z = 280 (parent).

To a solution of 4,6-diphenyl-5-oxamino-2-oxo-piperidine (700 mg, 2.5 mmol) was added ca. 2 g of wet

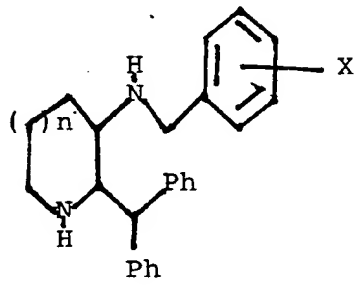
Raney nickel which had been washed with H_2O (until washings had a neutral pH) followed by ethanol, and the mixture was placed under an atmosphere of hydrogen (40 psi, Parr apparatus) overnight. The mixture was filtered through a pad of diatomaceous earth (Celite (trademark)), and the filter cake was rinsed well with ethanol. The filtrate was concentrated to afford 500 mg of 5-amino-4,6-diphenyl-2-oxopiperidine as a foam. ^1H NMR ($CDCl_3$) δ 2.96 (m, 4H), 4.12, 4.5 (m, 1H), 7.2 (m, 10H). Mass spectrum: m/z 266 (parent).

Under a nitrogen atmosphere in a round bottom flask were placed 500 mg (1.9 mmol) of 5-amino-4,6-diphenyl-2-oxopiperidine and 5 mL of methanol. To the system was added 1 g of 3 Å molecular sieves, and the pH of the mixture was adjusted to 4.5 using methanol saturated with HCl. To this system was added 284 mg (2.1 mmol) of 2-methoxybenzaldehyde, and the mixture was stirred at room temperature overnight. The mixture was filtered through diatomaceous earth (Celite (trademark)), the filter cake was rinsed well with methanol and the filtrate was concentrated with a rotary evaporator. The residue was partitioned between saturated aqueous sodium bicarbonate and chloroform, the layers were separated and the aqueous phase was extracted with three portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4) and concentrated, and the residue was subjected to flash column chromatography (30 g of silica gel) using 3:97 methanol/chloroform as the eluant to obtain 115 mg of 4,6-diphenyl-5-(2-methoxybenxylamino)-2-oxopiperidine. ^1H NMR ($CDCl_3$) δ 2.36 (dd, 1H, J = 6, 18), 2.99 (m, 2H), 3.30 (m, 1H), 3.35 (s, 3H), 3.62 (d, 1H, J = 16), 3.74 (d, 1H, J = 16), 4.22 (m, 1H), 6.62 (d, 1H, J = 6), 6.80 (t, 1H, J = 6), 6.96 (m, 3H), 7.18 (m, 10H). Mass spectrum: m/z 386 (parent).

Under a nitrogen atmosphere in a round-bottom flask were placed 115 mg (0.3 mmol) of the amine 4,6-diphenyl-5-(2-methoxybenzylamino)-2-oxopiperidine and 5 mL of THF. To the system was added 0.74 mL (1.5 mmol) of 2.0 M borane-methyl sulfide complex in THF, and the reaction mixture was heated at 60°C overnight. The mixture was cooled to room temperature, and methanol was added carefully to the system. The mixture was stirred for 2 hours and concentrated with a rotary evaporator. To this system were added 83 mg (0.6 mmol) of potassium carbonate and ca. 3 mL of ethanol, and the mixture was heated at 85°C for 3 hours. The mixture was cooled to room temperature, concentrated, partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate and extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2 fractions were dried (Na_2SO_4) and concentrated to obtain 109 mg of an oil. This crude material was subjected to flash column chromatography (5 g of silica gel) using 1:19 methanol/chlorform as the eluant to afford 56 mg of the title compound. The hydrochloride salt of this material was prepared by treating a CH_2Cl_2 solution of the product with ether saturated with HCl, concentrating, triturating with ether, scratching and repeating the concentration from ether. M.p. 176-178°C (HCl salt, dec).

^1H NMR ($CDCl_3$) δ 7.18 (m, 11H), 6.92 9 (d, 1H) = 6 Hz), 6.76 (t, 1H, J = 6 Hz), 6.61 (d, 1H, J = 6 Hz), 4.01 (d, 1H, J = 2 Hz), 3.66 (d, 1H, J = 12 Hz), 3.53 (d, 1H, J = 12 Hz), 3.38 (s, 3H), 3.30 (m, 1H), 3.12 (m, 3H), 2.12 (m, 2H). HRMS calc'd. for $C_{25}H_{28}N_2O$: 3.72.2202. Found: 372.2193.

The title compounds of Examples 21-26 have the following general formula



and were prepared by the following procedure.

A. Methyl 4-hydroxy-5-nitro-6,6-diphenyl hexanoate

A solution of 2,2-diphenyl-nitroethane (42.6 gm, 187 mmole) and potassium tert. butoxide (3.15 gm, 28 mmole) was stirred into a mixture of tetrahydrofuran and tert. butanol (1.5:1, 320 mL) at -78°C, and methyl 3-formyl-propionate (24.0 gm, 206 mmole) was added. The reaction mixture was then allowed to warm to 10°C over a period of 1 hour, after which it was quenched with acetic acid (1.8 ml). The mixture was concentrated under vacuum, diluted with pH 7 buffer (400 ml), and extracted with methylene chloride (3 x 400 ml). The combined extracts were dried (anhyd. $MgSO_4$), filtered and concentrated to afford an orange oil which on trituration with ether afforded methyl 4-hydroxy-5-nitro-6,6-diphenyl hexanoate (29.94 gm). The filtrate was concentrated and flash chromatographed. Elution with 10% ethyl acetate in hexane afforded an additional 20.66 gm of methyl 4-hydroxy-5-nitro-6,6-diphenyl hexanoate. Total yield (79%).

^1H NMR ($CDCl_3$) δ 7.2-7.4 (10H, m), 5.3 (1H, dd, J = 2.5, 12 Hz), 4.9 (1H, d, J = 12 Hz), 3.6 (3H, s), 2.6 (1H, m), 2.45 (2H, t, J = 7 Hz), 1.7-2.0 (1H, m), 1.6-1.7 (1H, m).

B. 2-Oxo-5-hydroxy-6-benzhydryl piperidine

To a stirred solution of methyl 4-hydroxy-5-nitro-6,6-diphenyl hexanoate (50.5 gm, 147 mmol) in ethanol (200 ml) at 25°C was added neutral Raney nickel (50 gms). The reaction mixture was shaken on a Parr shaker under hydrogen (30 psi). After 18 hours, the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) which was thoroughly washed with ethanol (400 ml) and methylene chloride (600 ml). The organic phases were combined and concentrated under vacuum to a yellow oil (40.25 gms), which on trituration with cold ether afforded 2-oxo-5-hydroxy-6-benzhydryl piperidine (18.5 gm, m.p. 208°C, 45%). Evaporation of the mother liquor afforded an oily residue upon treatment with potassium tert. butoxide in tetrahydrofuran at room temperature for 6 hours. Extraction with methylene chloride and trituration with ether afforded an additional 2.55 gms of 2-oxo-5-hydroxy-6-benzhydryl-piperidine (overall yield 51%).

IR (neat ν max 3380, 1640 cm^{-1})

^1H NMR ($CDCl_3$) δ 7.17-7.4 (10H, m), 5.49 (1H, bs), 4.18 (2H, s), 3.86 (1H, bs), 2.54-2.7 (1H, m), 2.3-2.42 (1H, m), 1.8-2.08 (2H, m).

HRMS Calc'd for $C_{18}H_{20}N_2O$: 282.1495. Found: 282.1495.

C. 2,5-Dioxo-6-benzhydrylpiperidine

To a stirred solution of 2-oxo-5-hydroxy-6-benzhydryl piperidine (18.15 gm, 64.5 mmole) in acetone (150 ml) at -5°C was added Jones reagent (2.67 M, 94 mmole), and the reaction mixture was further stirred for 4 hrs. At the end of this period, the excess reactant was decomposed with 2-propanol and the solution concentrated under vacuum to half of its volume. The contents of the flask were then diluted with water (1000 ml) and extracted with methylene chloride (3 x 1000 ml). The

combined organic phases were dried (anhy. $MgSO_4$) and the methylene chloride was removed under vacuum to afford 2,5-dioxo-6-benzhydrylpiperidine (15.35 gm, 85%).

^1H NMR ($CDCl_3$) δ 7.18-7.4 (10H, m), 4.8 (1H, d, J = 4Hz), 4.7 (1H, dd, J = 4, 1.6 Hz), 2.38-2.6 (2H, m), 2.16-2.3 (2H, m), 1.9-2.01 (1H, m).

D. 2-Oxo-5-oxamino-6-benzhydrylpiperidine

To a stirred solution of 2,5-dioxo-6-benzhydryl-piperidine (15.35 gm, 55 mmole) in pyridine (150 ml) was added hydroxylamine hydrochloride (10.63 gm, 165 mmole) and the reaction mixture was stirred for 15 min. The reaction mixture was concentrated under vacuum, and the contents were poured into 1N HCl (250 ml). The aqueous phase was extracted with methylene chloride (2 x 300 ml) and dried (anhyd. $MgSO_4$). The methylene chloride was removed under vacuum to afford 2-oxo-5-oxamino-6-benzhydrylpiperidine (10.62 gms, 65%).

^1H NMR ($CDCl_3$) δ 7.18-7.4 (10H, m), 5.96 (1H, bd), 5.59 (1H, bs), 4.8 (1H, m), 3.8 (1H, d, J = 10 Hz), 2.98-3.09 (1H, m), 2.05-2.42 (3H, m).

The title compounds of examples 21-26 were prepared from the title compound of "D" above by a procedure similar to that described in Examples 1(B) and 1(C).

EXAMPLE 21

Cis-3-benzylamino-2-benzhydrylpiperidine (X=H, n = 1) M.p. 117°C. ^1H NMR ($CDCl_3$) δ 7.0-7.4 (15H, m), 4.39 (1H, d, J = 10 Hz), 3.76 (1H, d, J = 12 Hz), 3.4 (1H, d, J = 12 Hz), 3.28 (1H, d, J = 10 Hz), 2.94 (1H, m), 2.54 (1H, m), 2.54 (1H, m), 2.0 (2H, m), 1.7 (1H, m), 1.22 (1H, m). HRMS Calc'd for $C_{25}H_{28}N_2$: 356.2253. Found: 356.2256.

EXAMPLE 22

Trans-3-benzylamino-2-benzhydrylpiperidine (X=H, n = 1) M.p. 186° (HCl salt). ^1H NMR ($CDCL_3$) δ 7.1-7.6 (15H,

m), 4.57 (1H, d, J = 10 Hz), 3.82 (1H, d, J = 14 Hz), 3.65 (1H, d, J = 14 Hz), 3.46 (1H, bt), 2.9 (1H, m), 2.5 (3H, m), 2.05 (1H, m), 1.72 (1H, m), 1.45 (1H, m). HRMS Calcd for $C_{25}H_{28}N_2$: 356.2253. Found: 356.2269.

EXAMPLE 23

Cis-3-(2-methoxybenzylamino)-2-benzhydrylpiperidine (x = 2-OMe, n = 1) M.p. 258°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 6.7-7.4 (14H, m), 4.4 (1H, d, J = 10 Hz), 3.8 (3H, s), 3.75 (2H, dd, J = 12 Hz), 3.45 (1H, bd), 3.39 (1H, d, J = 10 Hz), 3.0 (1H, bd), 2.62 (2H, m), 2.08 (1H, m), 1.7 (1H, m), 1.4 (1H, m), 1.2 (1H, m). HRMS Calc'd for $C_{26}H_{30}N_2O$: 386.2358. Found: 386.2358.

EXAMPLE 24

Trans-3-(2-methoxybenzylamino)-2-benzhydryl-piperidine (X = 2-OMe, n = 1) Oil. ^{1}H NMR ($CDCl_3$) δ 6.7-7.4 (14H, m), 4.55 (1H, d, J = 10 Hz), 3.8 (3H, s), 3.81 (1H, d, J = 14 Hz), 3.6 (1H, d, J = 14 Hz), 3.4 (1H, m), 2.9 (1H, m), 2.54 (2H, m), 2.0 (2H, m), 1.53 (1H, m), 1.45 (1H, m). HRMS Calcd for $C_{26}H_{30}N_2O$: 386.2358. Found: 386.2318.

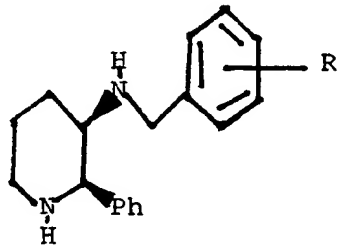
EXAMPLE 25

Cis-3-benzylamino-2-benzhydrylazepine (X=H, n = 2) M.p. 111-112°C. ^{1}H NMR ($CDCl_3$) δ 6.94-7.45 (15H, m), 4.33 (1H, d, J = 10 Hz), 3.52 (1H, d, J = 12 Hz), 3.34 (1H, d, J = 12 Hz), 3.21 (1H, dd, J = 2.1, 10 Hz), 3.16 (1H, bd), 2.4-2.58 (2H, m), 1.8 (1H, m), 1.56 (3H,m), 1.32 (2H, m).

EXAMPLE 26

Trans-3-benzylamino-2-benzhydrylazepine (X=H, n = 2) M.p. 186-187°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.0-7.5 (15H, m), 3.88 (1H, d, J = 11 Hz), 3.45-3.6 (2H, m), 3.22 (1H, d, J = 12 Hz), 3.0 (1H, d, J = 12 Hz), 2.45-2.62 (2H, m), 1.75 (1H, m), 1.5 (2H, m), 1.08-1.25 (3H, m). HRMS Calcd for $C_{26}H_{31}N_2$: 371.2487. Found: 371.2495.

The title compounds of Examples 27-33 have the following general formula and were prepared by a procedure similar to that of Example 1.



EXAMPLE 27

Cis-3-benzylamino-2-phenylpiperidine (R = H). M.p. 250°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 6.94-7.0 (10H, m), 3.89 (1H, d, J = 2.3 Hz), 3.52 (1H, d, J = 13 Hz), 3.32 (1H, d, J = 13 Hz), 3.25 (1H, bd, J = 12 Hz), 2.88 (1H, d, J = 2.5 Hz), 2.78 (1H, dt, J = 12, 3 Hz), 2.4 (1H, d, J = 12 Hz), 1.8-1.98 (1H, m), 1.6 (1H, tt, J = 12, 2.5 Hz), 1.42 (1H, d, J = 12 Hz).

EXAMPLE 28

Cis-3-(2-fluorobenzylamino)-2-phenylpiperidine (I, (R = 2-F). M.p. $>$ 260°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.31-7.2 (5H, m), 7.15-7.07 (1H, m), 6.97-6.85 (3H, m), 3.88 (1H, d, J = 3 Hz), 3.64 (1H, d, J = 14 Hz), 3.50 (1H, d, J = 14 Hz), 3.36-3.2 (1H, m), 2.87-2.73 (2H, m), 2.07 (1H, bd, J = 13 Hz), 1.88 (1H, qt, J = 13, 4 Hz), 1.67-1.58 (1H, m), 1.43 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 162.6, 159.4, 142.6, 130, 129.8, 128.2, 128, 127, 127.8, 127.6, 126.8, 126.4, 123.73, 123.7, 115, 114.7, 64.3, 55.5, 47.8, 44.5, 44.4, 29.1, 29.4. HRMS Calc'd for $C_{18}H_{21}N_2F$: 284.1689. Found: 284.1701.

EXAMPLE 29

Cis-3-(2,6-difluorobenzylamino)-2-phenylpiperidine (R = 2,6-di F). M.p. $>$ 260°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.33-7.02 (6H, m), 6.7 (2H, t, J = 8 Hz), 3.86 (1H, d, J = 2 Hz), 3.63 (1H, d, J = 14 Hz), 3.52 (1H, d,

J = 14 Hz), 3.24 (1H, bd, J = 10 Hz), 2.83-2.74 (1H, m), 2.09 (1H, bd, J = 13 Hz), 1.9 (1H, qt J = 14, 4 Hz), 1.63 (1H, tt, J = 14, 4 Hz), 1.4 (1H, bd, J = 12 Hz). ^{13}C NMR ($CDCl_3$) δ 142.1, 128.4, 128.3, 126.7, 126, 111.1, 110.8, 110.7, 63.8, 55.2, 47.7, 38.5, 28.9, 20.4. HRMS Calc'd for : 302.1595. Found: 302.1607.

EXAMPLE 30

Cis-3-(2-methylbenzylamino)-2-phenylpiperidine (R = 2-CH_3). M.p. 254°C. (dec., HCl salt). ^1H NMR ($CDCl_3$) δ 7.31-7.21 (4H, m), 7.09-6.96 (4H, m), 3.9 (1H, d, J = 2 Hz), 3.54 (1H, d, J = 14 Hz), 3.28 (1H, d, J = 14 Hz), 3.22-3.14 (1H, m), 2.91-2.87 (1H, m), 2.79 (1H, td, J = 8, 4 Hz), 2.14 (1H, bd, J = 9 Hz), 1.98 (3H, s), 1.97-1.75 (1H, m), 1.7-1.48 (3H, m). ^{13}C NMR ($CDCl_3$) δ 142.7, 138.6, 136.4, 130, 128.4, 128.2, 126.7, 126.6, 125.5, 64.3, 56.2, 49.7, 29.3, 20.5, 18.5. HRMS Calc'd for $C_{19}H_{24}N_2$: 280.1939. Found: 280.1952.

EXAMPLE 31

Cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine (R = 2-CF_3). M.p. 249°C (dec., HCl salt). ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, J = 8 Hz), 7.49-7.16 (8H, m), 3.89 (1H, d, J = 2 Hz), 3.7 (1H, d, J = 15 Hz), 3.57 (1H, d, J = 15 Hz), 3.25 (1H, bd, J = 12 Hz), 2.86-2.74 (2H, m), 2.08 (1H, bd, J = 12 Hz), 1.93-1.8 (1H, m), 1.67-1.55 (2H, m), 1.44 (1H, bd, J - 14 Hz). ^{13}C NMR ($CDCl_3$) δ 142.7, 139.8, 131.5, 129.7, 128.2, 126.8, 126.5, 126.2, 125.4, 125.4, 64.6, 56.2, 47.8, 47.0, 29, 20.5. HRMS Calc'd for $C_{19}H_{21}N_2F_3$: 334.1657. Found: 334.1665.

EXAMPLE 32

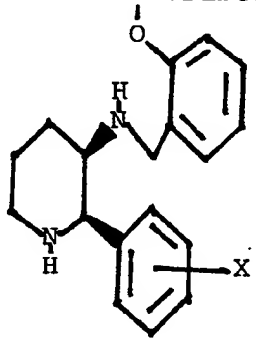
Cis-3-(2-chlorobenzylamino)-2-phenylpiperidine (R = 2-Cl). M.p. 256°C (dec., HCl salt). ^1H NMR ($CDCl_3$) δ 7.31-6.97 (9H, m), 3.88 (1H, d, J = 2 Hz), 3.63 (1H, d, J = 15 Hz), 3.48 (1H, d, J = 15 Hz), 3.25 (1H, bd, J = 10 Hz), 2.87-2.74 (2H, m), 2.09 (1H, bd, J = 15 Hz), 1.9 (1H, qt, J = 13, 4 Hz), 1.68-1.57 (1H, m), 1.43 (1H, bd,

J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 142.5, 138.1, 133.6, 129.7, 129.1, 128.3, 127.7, 126.8, 126.4, 64.3, 55.6, 48.7, 47.8, 29, 20.4 HRMS Calc'd for $C_{18}H_{21}N_2Cl$: 300.1394. Found: 300.1394.

EXAMPLE 33

Cis-3-(3-trifluoromethylbenzylamino)-2-phenyl-piperidine (R = 3-CF_3). M.p. 240°C (dec., HCl salt). ^1H-NMR ($CDCl_3$) δ 7.41-7.14 (9H, m), 3.88 (1H, d, J = 2 Hz), 3.55 (1H, d, J = 14 Hz), 3.38 (1H, d, J = 14 Hz), 3.22 (1H, bd, J = 14 Hz), 2.84-2.74 (2H, m), 2.01 (1H, bd, J = 14 Hz), 1.85 (1H, qt, J = 12, 4 Hz), 1.63-1.54 (1H, m), 1.45 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 142.8, 142.1, 131.1, 128.4, 128.3, 127, 126.4, 124.5, 123.3, 123.3, 64.5, 55.8, 51, 47.7, 29.4, 20.4. HRMS Calc'd for $C_{19}H_{21}N_2F_3$: 334.1657: Found: 334.1663.

The title compounds of examples 34-55 have the following general formula and were prepared by a procedure similar to that described in Example 1.



EXAMPLE 34

Cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine (X = 2-F). M.p. 253°C (HCl salt). ^1H NMR ($CDCl_3$) δ 8.03 (1H, t, J = 7 Hz), 7.62-7.54 (1H, m), 7.47-7.35 (2H, m), 7.27-7.19 (2H, m), 6.94 (2H, dd, J = 9, 2 Hz), 5.25 (1H, d, J = 4 Hz), 5.25 (1H, d, J = 13 Hz), 4.03-4.00 (1H, m), 3.87 (1H, d, J = 13 Hz), 3.75 (3H, s), 3.67 (1H, bd, J = 13 Hz), 3.42-3.37 (2H, m),

2.6-2.42 (2H, m), 2.38-2.3 (1H, m), 2.08-1.96 (1H, m). HRMS Calcd for $C_{19}H_{23}N_2OF$: 314.1795. Found: 314.1778.

EXAMPLE 35

Cis-3-(2-methoxybenzylamino)-2-(2-chlorophenyl)-piperidine (X = 2-Cl). M.p. 264°C (HCl salt). ^1H NMR ($CDCl_3$) δ 8.15 (1H, d, J = 6 Hz), 7.66-7.5 (1H, m), 7.39 (1H, t, J = 8 Hz), 7.15 (1H, d, J = 6 Hz), 6.94 (2H, t, J = 8 Hz), 5.21 (1H, d, J = 3 Hz), 4.19-4.1 (2H, m), 3.27 (1H, d, J = 12 Hz), 3.78 (3H, s), 3.76-3.64 (1H, m), 3.52-3.4 (1H, m), 2.64-2.44 (2H, m), 2.38-2.26 (1H, m), 2.16-1.96 (1H, m). HRMS Calc'd for $C_{19}H_{23}N_2OCl$: 330.1499. Found: 330.1412

EXAMPLE 36

Cis-3-(2-methoxybenzylamino)-2-(2-methylphenyl)-piperidine (X = 2-CH_3). M.p. 260°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.97 (1H, bd, J - 8 Hz), 7.49-7.32 (4H, m), 7.08 (1H, d, J = 6 Hz), 6.95-6.88 (2H, m), 5.04 (1H, d, J = 3 Hz), 4.1 (1H, d, J = 14 Hz), 3.88-3.8 (2H, m), 3.68 (3H, s), 3.49-3.36 (1H, m), 2.59-2.27 (4H, m), 2.25 (3H, s), 2.0 (1H, bd, J = 10 Hz). HRMS Calc'd for $C_{20}H_{26}N_2O$: 310.2045. Found: 310.2080. C, 62.66; H, 7.36; N, 7.31. Found: C, 62.75; H, 7.46; N, 7.2.

EXAMPLE 37

Cis-3-(2-methoxybenzylamino)-2-(3-trifluorophenyl)-piperidine (X = 3-CF_3). M.p. 268°C (HCl salt). ^1H NMR ($CDCl_3$) δ 8.03-7.94 (2H, m), 7.84 (1H, d, J = 8 Hz), 7.77 (1H, t, J = 8 Hz), 7.37 (1H, t, J = 8 Hz), 7.16 (1H, d, J = 8 Hz), 6.93 (2H, t, J = 7 Hz), 5.05 (1H, d, J = 2 Hz), 4.14 (1H, d, J = 13 Hz), 3.86 (1H, d, J = 13 Hz), 3.72 (3H, s), 3.7-3.62 (1H, m), 3.3-3.2 (1H, m), 2.49-2.34 (2H, m), 2.3-2.18 (1H, m), 2.01 (1H, bd, J = 14 Hz).

EXAMPLE 38

Cis-3-(2-methoxybenzylamino)-2-(3-fluorophenyl)-piperidine (X = 3-F). M.p. 264°C (HCl salt). ^1H NMR

($CDCl_3$) 7.62-7.5 (3H, m), 7.38 (1H, t, J = 7 Hz), 7.3-7.21 (2H, m), 6.93 (2H, t, J = 8 Hz), 5.03 (1H, d, J = 3 Hz), 4.16 (1H, d, J = 15 Hz), 4.06-3.96 (1H, m), 3.85 (1H, d, J = 13 Hz), 3.75 (3H, s), 3.66 (1H, bd, J = 12 Hz), 2.47-2.40 (2H, m), 2.30-2.15 (1H, m), 2.06-1.92 (1H, m). HRMS Calc'd for $C_{19}H_{23}N_2OF$: 314.1795. Found: 314.1790.

EXAMPLE 39

Cis-3-(2-methoxybenzylamino)-2-(3-chlorophenyl)-piperidine (X = 3-Cl). M.p. 258-260°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.72 (1H, bs), 7.7-7.58 (1H, m), 7.54 (2H, d, J = 4 Hz), 7.4 (1H, t, J = 8 Hz), 7.2 (1H, d, J = 7 Hz), 6.97-6.92 (2H, m), 5.01 (1H, d, J = 4 Hz), 4.17 (1H, d, J = 13 Hz), 3.99 (1H, bs), 3.88 (1H, d, J = 13 Hz), 3.75 (3H, s), 3.69-3.54 (1H, m), 3.17-3.14 (1H, m), 2.49-2.4 (2H, m), 2.3-2.16 (1H, m), 2.05-1.94 (1H, m). HRMS Calc'd for $C_{19}H_{23}N_2OCl$: 330.1499. Found: 330.1508.

EXAMPLE 40

Cis-3-(2-methoxybenzylamino)-2-(3-methoxyphenyl)-piperidine (X = 3-OMe). M.p. 252°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.49-7.34 (2H, m), 7.28-7.16 (3H, m), 7.07 (1H, d, J - 6 Hz), 6.96-6.91 (2H, m), 4.94 (1H, d, J = 4 Hz), 4.15 (1H, d, J = 13 Hz), 3.96 (1H, bs), 3.86 (1H, d, J = 13 Hz), 3.83 (3H, s), 3.69 (3H, s), 3.68-3.6 (1H, m), 3.28-3.22 (1H, m), 2.49-2.35 (2H, m), 2.32-2.16 (1H, m), 2.06-1.94 (1H, m). HRMS Calc'd for $C_{20}H_{26}N_2O_2$: 326.1994. Found: 326.1983. C, 60.15; H, 7.07; N, 7.01. Found: C, 59.78; H, 6.75; N, 7.01.

EXAMPLE 41

Cis-3-(2-methoxybenzylamino)-2-(3-methylphenyl)-piperidine (X = 3-CH_3). M.p. 243°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.15 (2H, dd, J = 8.7 Hz), 7.07-6.94 (4H, m), 6.79 (1H, t, J = 7 Hz), 6.67 (1H, d, J = 8 Hz), 3.83 (1H, d, J = 2 Hz), 3.68 (1H, d, J = 14 Hz), 3.44 (3H,s), 3.4

(1H, d, J = 14 Hz), 3.26 (1H, bd, J = 12 Hz), 2.85-2.73 (1H, m), 2.3 (3H, s), 2.12 (1H, bd, J = 14 Hz), 1.92 (1H, qt, J = 13, 4 Hz), 1.58 (1H, tt, J = 14 Hz), 1.38 (1H, bd, J = 13 Hz). HRMS Calc'd for $C_{20}H_{26}N_2O$: 310.2045. Found: 310.2069. C, 62.66; H, 7.36; N, 7.31. Found: C, 62.61; H, 7.44; N, 7.24.

EXAMPLE 42

Cis-3-(2-methoxybenzylamino)-2-(4-biphenyl)-piperidine (X = 4-Ph). M.p. 255°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.77-7.7 (4H, m), 7.63-7.44 (3H, m), 7.41 (2H, t, J = 2 Hz), 7.39-7.31 (2H, m), 7.15 (1H, dd, J = 6, 2 Hz), 6.92 (1H, t, J = 7 Hz), 6.79 (1H, d, J = 8 Hz), 5.03 (1H, bs), 4.13 (1H, d, J = 13 Hz), 3.87 (2H, d, J = 13 Hz), 3.6 (4H, s), 3.34-3.3 (2H, bs), 2.58-2.1 (3H, m), 2.00-1.89 (1H, m). HRMS Calc'd for $C_{25}H_{28}N_2O$: 372.2202. Found: 372.2220.

EXAMPLE 43

Cis-3-(2-methoxybenzylamino)-2-(4-fluorophenyl)-piperidine (X = 4-F). M.p. 252°C (HCl salt). IR (KBr) ν max 3280, 2600, 1605, 1520, 1240, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.25-7.12 (3H, m), 6.99-6.94 (3H,m), 6.8 (1H, t, J = 6 Hz), 6.68 (1H, d, J = 8 Hz), 3.83 (1H, bs), 3.67 (1H, d, J = 14 Hz), 3.49 (3H, s), 3.38 (1H, d, J = 14 Hz),3.26-3.2 (1H, m), 2.82-2.71 (2H, m), 2.11 (1H, bd, J = 13 Hz), 1.97 -1.83 (1H, m), 1.63-1.52 (1H, m), 1.38 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 157.6, 138.3, 129.6, 128.3, 127.9, 127.8, 120, 114.9, 114.6, 109.8, 63.4, 54.8, 54.6, 47.8, 46.7,28.2, 20.3. HRMS Calc'd. for $C_{19}H_{23}N_2OF$: 314.1795. Found: 314.1802.

EXAMPLE 44

Cis-3-(2-methoxybenzylamino)-2-(4-methylphenyl)-piperidine (X = 4-CH_3). M.p. 233°C (HCl salt). IR (KBr) ν max 3400, 2700, 1610, 1570, 1460, 1260, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.18-7.11 (5H, m) 6.97 (1H, dd, J = 7, 2 Hz), 6.79 (1H, t, J = 8 Hz), 6.67 (1H, d, J = 8

Hz), 3.84 (1H, d, J = 2 Hz), 3.67 (1H, d, J = 14 Hz), 3.45 (3H, s), 3.4 (1H, d, J= 14 Hz), 3.25 (1H, bd, J = 8 Hz), 2.82-2.73 (2H, m), 2.31 (3H, s), 2.11 (1H, bd, J = 13 Hz), 1.91 (1H, qt, J = 9, 4 Hz), 1.57 (1H, tt, J = 14, 4 Hz), 1.37 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 157.6, 139.4, 135.9, 129.6, 128.8, 128.4, 127.7, 126.2, 120, 109.8, 63.7, 54.8, 54.7, 47.8, 46.7, 28.2, 21.0, 20.4. HRMS Calcd for $C_{20}H_{26}N_2O$: 310.2045. Found: 310.2043.

EXAMPLE 45

Cis-3-(2-methoxybenzylamino)-2-(4-chlorophenyl)-piperidine (X = 4-Cl). M.p. 247°C (HCl salt). IR (KBr) ν max 2950, 2640, 1610, 1570, 1500, 1450, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.26-7.13 (5H, m), 6.97 (1H, dd, J = 7, 2 Hz), 6.81 (1H, t, J = 8 Hz), 6.68 (1H, d, J = 8 Hz), 3.84 (1H, d, J = Hz), 3.7 (1H, d, J = 14 Hz), 3.48 (3H, s), 3.37 (1H, d, J = 14 Hz), 3.26 (1H, bd, J = 8 Hz), 2.83-2.72 (2H, m), 2.12 (1H, bd, J = 9 Hz), 1.91 (1H, qt, J = 13, 4 Hz), 1.58 (1H, tt, J = 13, 4 Hz), 3.83 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 157.6, 140.6, 132.4, 129.7, 128.2, 128, 127.7, 120, 109.9, 63.3, 54.8, 54.5, 47.7, 46.8, 28, 20. HRMS Calc'd for $C_{19}H_{23}N_2OCl$: 330.1498. Found: 330.1489. C, 56.52; H, 6.24; N, 6.94. Found: C, 56.52; H, 6.2; N, 6.86.

EXAMPLE 46

Cis-3-(2-methoxybenzylamino)-2-(4-methoxyphenyl)-piperidine (X = 4-OMe). M.p. 245°C (HCl salt). ^1H NMR ($CDCl_3$) δ 7.14 (3H, t, J = 8 Hz), 6.97 (1H, dd, J = 7, 2 Hz), 6.84-6.77 (3H, m), 6.67 (1H, d, J = 8 Hz), 3.81 (1H, d, J = 2 Hz), 3.78 (1H, s), 3.67 (1H, d, J = 14 Hz), 3.47 (3H, s), 3.4 (1H, d, J = 14 Hz), 3.24 (1H, bd, J = 10 Hz), 2.81-2.72 (2H, m), 2.1 (1H, bd, J = 14 Hz), 1.9 (1H, qt, J = 14, 4 Hz), 1.56 (1H, tt, J = 14, 4 Hz), 1.36 (1H, bd, J = 14 Hz). ^{13}C NMR ($CDCl_3$) δ 158.3, 157.6, 134.6, 129.6, 128.4, 127.7, 127.3, 120, 113.5, 109.8 63.4, 55.2,

54.8, 54.7, 47.8, 46.7, 28.2, 20.3. HRMS Calc'd for $C_{20}H_{26}N_2O_2$: 326.1996. Found: 326.1968. C, 60.15, H, 7.07; N, 7.01. Found: C, 59.36; H, 6.79; N, 6.82.

EXAMPLE 47

Cis-3-(2-methoxybenzylamino)-2-(4-trifluoromethyl-phenyl)-piperidine (X = 4-CF_3). M.p. 250°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, d, J = 8 Hz), 7.33 (2H, d, J = 8 Hz), 7.13 (1H, t, J = 8 Hz), 6.93 (1H, d, J = 8 Hz), 6.77 (1H, t, J = 8 Hz), 6.63 (1H, d, J = 8 Hz), 3.89 (1H, s), 3.67 (1H, d, J = 14 Hz), 3.39 (3H, s), 3.33 (1H, d, J = 14 Hz), 3.24 (1H, bd, J = 12 Hz), 2.82-2.74 (2H, m), 2.13 (1H, bd, J = 14 Hz), 1.98-1.78 (1H, m), 1.64-1.46 (1H, m), 1.38 (1H, bd, J = 14 Hz). ^{13}C NMR ($CDCl_3$) δ 157.4, 146.5, 129.5, 127.8, 126.5, 124.8, 124.7, 119.8, 109.7, 63.6, 54.4, 54.3, 47.5, 46.6, 28, 10. HRMS Calcd for $C_{20}H_{23}N_2OF_3$: 364.1762. Found: 364.1710.

EXAMPLE 48

Cis-3-(2-methoxybenzylamino)-2-(4-bromophenyl)-piperidine (X = 4-Br). M.p. 250°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.36 (2H, d, J = 8 Hz), 7.14-7.05 (3H, m), 6.95 (1H, dd, J = 8, 2 Hz), 6.79 (1H, t, J = 8 Hz), 6.67 (1H, d, J = 8 Hz), 3.79 (1H, d, J = 2 Hz), 3.66 (1H, d, J = 14 Hz), 3.48 (3H, s), 3.34 (1H, d, J = 14 Hz), 3.22 (1H, bd, J = 14 Hz), 2.78-2.68 (2H, m), 2.17 (1H, bd, J = 14 Hz), 1.96-1.78 (1H, m), 1.56 (1H, tt, J = 14, 4 Hz), 1.38 (1H, bd, J = 14 Hz). ^{13}C NMR ($CDCl_3$) δ 157.6, 141.4, 131.1, 129.7, 128.1, 128, 127.9, 120.4, 120, 109.8, 63.4, 54.8, 54.4, 47.6, 46.8, 28.1, 20.2. HRMS Calc'd for $C_{19}H_{23}N_2OBr$: 374.0980. Found: 374.0926. C, 50.91; H, 5.62; N, 6.25. Found: C, 51.41; H, 5.48; N, 6.23.

EXAMPLE 49

Cis-3-(2-methoxybenzylamino)-2-(4-hydroxymethyl-phenyl)-piperidine (X = 4-CH_2OH). M.p. 248°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.2-7.04 (5H, m), 6.95 (1H, dd, J = 8, 2

Hz), 6.7 (1H, t, J = 8 Hz), 6.64 (1H, d, J = 8 Hz), 4.6 (2H, s), 3.82 (1H, d, J = 2 Hz), 3.62 (1H, d, J = 14 Hz), 3.43 (3H, s), 3.37 (1H, d, J = 14 Hz), 3.24 (1H, bd, J = 8 Hz), 2.8-2.68 (2H, m), 1.96-1.8 (1H, m), 1.56 (1H, tt, J = 14, 4 Hz), 1.36 (1H, bd, J = 8 Hz). HRMS Calc'd for $C_{20}H_{26}N_2O_2$: 326.1994. Found: 326.1979. C, 60.15; H, 7.07; N, 7.02. Found: C, 60.04; H, 6.93; H, 6.83.

EXAMPLE 50

Cis-3-(2-methoxybenzylamino)-2-(3-fluoro-4-methoxyphenyl)-piperidine (X = 3-F, 4-OMe). M.p. 250°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.15 (1H, dt, J = 8, 2 Hz), 7.01-6.93 (3H, m), 6.89-6.78 (2H, m), 6.7 (1H, d, J = 8 Hz), 3.87 (3H, s), 3.78 (1H, d, J = 2 Hz), 3.68 (1H, d, J = 14 Hz), 3.52 (3H, s), 3.38 (1H, d, J = 14 Hz), 3.22 (1H, bd, J = 9 Hz), 2.75 (2H, td, J = 13, 3 Hz), 2.1 (1H, bd, J = 13 Hz), 1.86 (1H, qt, J = 13, 4 Hz), 1.56 (1H, tt, J = 13, 3 Hz), 1.35 (1H, bd, J = 13 Hz). ^{13}C NMR ($CDCl_3$) δ 157.6, 135.8, 129.7, 128.2, 128, 121.8, 121.7, 120, 114.3, 114.1, 113, 109.8, 63, 56.3, 54.7, 54.5, 47.7, 46.8, 28.2, 20.3

EXAMPLE 51

Cis-3-(2-methoxybenzylamino)-2-(2,3-difluoro-phenyl)-piperidine (X = 2,3-diF). M.p. 243°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.21-7.12 (2H, m), 7.09-7.01 (1H, m), 6.98 (1H, dd, J = 7.2 Hz), 6.81 (1H, t, J = 7 Hz), 6.69 (1H, d, J = 8 Hz), 4.17 (1H, s), 3.61 (1H, d, J = 14 Hz), 3.54 (3H, s), 3.36 (1H, d, J = 14 Hz), 3.23 (1H, d, J = 14 Hz), 2.89 (1H, bs), 2.79 (1H, td, J = 12, 3 Hz), 2.03 (1H, bd, J = 13 Hz), 1.85 (1H, qt, J = 13, 4 Hz), 1.68-1.56 (1H, m), 1.41 (1H, bd, J = 14 Hz). ^{13}C NMR ($CDCl_3$) δ 157.5, 132.6, 132.4, 129.5, 128.3, 127.9, 123.6, 122.8, 120.2, 115.3, 115.1, 109.9, 58.3, 54.8, 53.2, 47.1, 28.6, 20.4.

EXAMPLE 52

Cis-3-(2-methoxybenzylamino)-2-(2,3-dichlorophenyl)-piperidine (X = 2,3-diCl). M.p. 249°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.42 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.19 (1H, t, J = 8 Hz), 7.14 (1H, t, J = 8 Hz), 6.91 (1H, d, J = 8 Hz), 6.79 (1H, t, J = 8 Hz), 6.68 (1H, d, J = 8 Hz), 4.19 (1H, d, J = 2 Hz), 3.55 (1H, d, J = 12 Hz), 3.53 (3H, s), 3.32 (1H, d, J = 14 Hz), 3.23 (1H, bd, J = 12 Hz), 3.03-2.98 (1H, m), 2.81 (1H, td, J = 13, 3 Hz), 2.01 (1H, bd, J = 13 Hz), 1.97-1.75 (1H, m), 1.7-1.62 (1H, m), 1.42 (1H, bd, J = 12 Hz).

EXAMPLE 53

Cis-3-(2-methoxybenzylamino)-2-(4-ethylaminophenyl)-piperidine (X = 4-NEt). M.p. 241°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.14 (1H, t, J = 8 Hz), 7.08-6.94 (3H, m), 6.78 (1H, t, J = 8 Hz), 6.67 (1H, d, J = 8 Hz), 6.52 (2H, d, J = 8 Hz), 3.77 (1H, bs), 3.69 (1H, d, J = 14 Hz), 3.5 (3H, s), 3.43 (1H, d, J = 14 Hz), 3.33 (1H, bd, J = 2 Hz), 3.12 (1H, q, J = 8 Hz), 2.84-2.68 (1H, m), 2.09 (1H, bd, J = 4 Hz), 1.96-1.49 (1H, m), 1.61-1.49 (1H, m), 1.35 (1H, bd, J = 14 Hz), 1.25 (3H, t, J = 8 Hz).

EXAMPLE 54

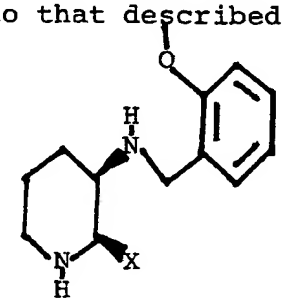
Cis-3-(2-methoxybenzylamino)-2-(3-methyl-4-methoxy-phenyl)-piperidine (X = 3-Me, 4-OMe). M.p. 248°C (HCl salt). IR (KBr) γ max 3540, 2600, 1610, 1560, 1460, 1270, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.13 (1H, t, J = 8 Hz), 7.02 (1H, d, J = 8 Hz), 6.94-6.9 (2H, m), 6.74 (1H, t, J = 8 Hz), 6.7 (1H, d, J = 8 Hz), 6.64 (1H, d, J = 8 Hz), 3.79 (3H, s), 3.78 (1H, s), 3.67 (1H, d, J = 1 Hz), 3.43 (3H, s), 3.38 (1H, d, J= 14 Hz), 3.21 (1H, bd, J = 14Hz), 2.14 (3H, s), 2.11-2.07 (1H, m), 1.93-1.74 (1H, m), 1.59-1.53 (1H, m), 1.38-1.33 (1H, m). ^{13}C NMR ($CDCl_3$) δ 157.6, 156.5, 134.1, 129.6, 128.6, 128.4, 127.7, 126.1, 124.4, 119.9, 109.7, 109.6, 63.3, 55.4, 54.7, 53.4, 47.8, 46.6, 28.1, 20.4, 16.3. HRMS Calc'd

for $C_{21}H_{28}N_2O_2$: 340.2151. Found: 340.2172.

EXAMPLE 55

Cis-3-(2-methoxybenzylamino)-2-(2-fluoro-6-chlorophenyl)-piperidine (X = 2-F, 6-Cl). M.p. 245-246°C (HCl salt). IR (KBr) νmax 3280, 2700, 1610, 1580, 1500, 1450, 1260, 1010 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.16-7.1 (3H, m), 6.99-6.82 (2H, m), 6.79 (1H, t, J = 8 Hz), 6.68 (1H, d, J = 8 Hz), 4.37 (1H, d, J = 2 Hz), 3.68 (1H, d, J = 14 Hz), 3.55 (1H, s), 3.47 (1H, d, J = 14 Hz), 3.2 (1H, bd, J = 14 Hz), 2.87-2.78 (1H, m), 2.7 (1H, t, J = 14 Hz), 2.4-2.0 (1H, m), 1.84-1.6 (2H, m), 1.36 (1H, bd, J = 14 Hz). ^{13}C NMR ($CDCl_3$) δ 157.4, 129.3, 128.3, 128.2, 127,8, 125.7, 125.6, 120.3, 115.4, 115, 109.9, 62.8, 62.8, 54.9, 53, 47.9, 47.3, 28.6, 20.8. HRMS Calc'd for $C_{19}H_{22}N_2OClF$: 348.1405. Found: 348.1369.

The title compounds of Examples 56-60 have the following general formula and were prepared by a procedure similar to that described in Example 1.



EXAMPLE 56

3-(2-Methoxybenzylamino)-piperidine (X = H). M.p. 198°C (HCl salt). ^{1}H NMR (HCl salt CD_3OH) δ 7.48 (2H, t, J = 6 Hz), 7.12 (1H, d, J = 6 Hz), 7.04 (1H, t, J = 8 Hz), 4.33 (2H, a, J = 4 Hz), 3.95 (3H, s), 3.8 (1H, bd, J = 9 Hz), 3.7-3.54 (1H, m), 3.41 (1H, bd, J = 9 Hz), 3.25 (1H, t, J = 12 Hz), 3.18-3.01 (1H, m), 2.48-2.4 (1H, m),

2.24-2.1 (1H, m), 2.01-1.79 (1H, m). HRMS Calc'd for $C_{13}H_{22}N_2O$: 220.1576. Found: 220.1587.

EXAMPLE 57

Cis-3-(2-methoxybenzylamino-)-2-(5-indanyl)-piperidine (X = 5-indane). M.p. 243°C (HCl salt). ^{1}HNMR ($CDCl_3$) δ 7.24-7.11 (3H, m), 6.97 (2H, t, J = 8 Hz), 6.79 (1H, t, J = 8 Hz), 6.65 (1H, d, J = 8 Hz), 3.83 (1H, bs), 3.68 (1H, d, J = 14 Hz), 3.43 (3H, s), 3.39 (1H, d, J = 14 Hz), 2.23 (1H, bd, J = 14 Hz), 2.88-2.72 (6H, m), 2.13-1.86 (5H,m), 1.56 (1H, tt, J = 13, 4 Hz), 1.37 (1H, bd, J = 14 Hz).

EXAMPLE 58

Cis-3-(2-methoxybenzylamno)-2-(1-naphthyl)-piperidine (X = 1-naphthyl). M.p. 251°C (HCl salt). ^{1}HNMR (HCl salt, CD_3OH) δ 8.16 (1H, d, J = 6 Hz), 8.08 (1H, d, J = 7 Hz), 8.04-7.98 (1H, m), 7.94-7.86 (1H, m), 7.71 (1H, t, J = 8 Hz), 7.64-7.61 (^{1}H, m), 7.17 (1H, t, J = 8 Hz), 6.84 (1H, d, J = 6 Hz), 6.66 (2H, t, J = 8 Hz), 5.73 (1H, bs), 4.06-3.99 (1H, m), 3.8-3.74 (2H, m), 3.49-3.4 (4H, m), 2.72-2.44 (3H, m), 6.84 (1H, bd, J = 8 Hz). HRMS Calc'd for $C_{23}H_{26}N_2O$: 346.2045. Found: 346.2062.

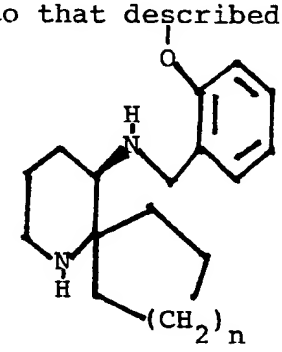
EXAMPLE 59

Cis-3-(2-methoxybenzylamino)-2-(2-naphthyl)-piperidine (X = 2-naphthyl). M.p. $>$250°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.87-7.78 (3H,m), 7.69 (1H, d, J = 8 Hz), 7.5-7.39 (2H, m), 7.14 (1H, d, J = 8 Hz), 7.1 (1H, t, J = 8 Hz), 6.92 (1H, d, J = 8 Hz), 6.75 (1H t, J = 8 Hz), 6.47 (1H, d, J = 8 Hz), 4.02 (1H, d, J = 2 Hz), 3.66 (1H, d, J = 14 Hz), 3.37-3.2 (2H, m), 2.97 (3H, s), 2.89 (1H, bs), 2.88-2.79 (1H, m), 2.16 (1H, bd, J = 14 Hz), 1.98 (1H, qt, J = 8, 3 Hz), 1.63 (1H, tt, J = 4, 12 Hz), 1.43 (1H, bd, J = 13 Hz).

EXAMPLE 60

Cis-3-(2-methoxybenzylamino)-2-cyclopentyl-piperidine (X = cyclopentyl). M.p. 161°C (HCl salt). IR (KBr) ν max 3480, 3420, 2960, 1610, 1500, 1260, 1020 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 7.48 (1H, d, J = 8 Hz), 7.17 (1H, t, J = 8 Hz), 6.9 (1H, t, J = 8 Hz), 6.8 (1H, d, J = 8 Hz), 3.78 (3H, s), 3.67 (1H, d, J = 13 Hz), 3.57 (1H, d, J = 13 Hz), 2.97 (1H, bd, J = 13 Hz), 2.69-2.64 (2H, m), 2.47 (1H, t, J = 9 Hz), 2.3-2.2 (2H, m), 1.75 (1H, bd, J = 9 Hz), 1.6-1.16 (7H, m), 1.0-0.9 (1H, m). ^{13}C NMR ($CDCl_3$) δ 157.9, 130.6, 128.5, 127.5, 120.2, 110, 61.3, 59.2, 55.1, 47.9, 47.2, 39, 29.2, 27.3, 26.2, 25.8, 24.1, 23.1. HRMS Calc'd for $C_{18}H_{28}N_2O$: 288.2201. Found: 288.2172.

The title compounds of Example 61-62 have the following general formula and were prepared by a procedure similar to that described in Example 1.



EXAMPLE 61

5-(2-Methoxybenzylamino)-1-aza-spiro[5.5]undecane (n = 2) M.p. 257°C (HCl salt). IR (KBr) ν max 2940, 1605, 1580, 1500, 1460, 1250, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.27-7.18 (2H, m), 6.89 (1H, t, J = 8 Hz), 6.84 (1H, d, J = 8 Hz), 3.86 (1H, d, J = 14 Hz), 3.82 (3H, s), 3.68 (1H, d, J = 14 Hz), 2.74-2.68 (2H, m), 2.25-2.08 (1H, m), 1.81=1.25 (13H, m). HRMS Calc'd for $C_{18}H_{28}N_2O$: 288.2202. Found 288.2182.

EXAMPLE 62

10-(2-methoxybenzylamino)-6-aza-spiro[4.5]decane (n = 1). M.p. 247°C (HCl salt). IR (KBr) ν max 2960, 2700, 1605, 1580, 1500, 1480, 1260, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.23-7.18 (2H, m), 6.89 (1H, t, J = 8 Hz), 6.84 (1H, d, J = 8 Hz), 3.89 (1H, d, J = 14 Hz), 3.83 (3H, s), 3.66 (1H, d, J = 14 Hz), 2.76-2.7 (2H, m), 2.31 (1H, dd, J = 8, 3 Hz), 1.81-1.24 (12H, m). HRMS Calc'd for $C_{17}H_{26}N_2O$; 274.2085. Found: 274.2057.

EXAMPLE 63

Cis-3-(2-methoxybenzylamino)-2-phenylpipieridne

A. 4-Phenyl-1-(tert.-butyldimethylsilyl)azeditin-2-one

4-Phenylazetidin-2-one (10.4 gm, 71.0 mmole) (Graf, Chem. Ber, 111 (1963); Durst et al. J. Org. Chem., 35, 2043 (1970)) was dissovled in DMF (200 ml) and was treated with tert.-butyldimethylsilyl chloride (12.8 gm, 85 mmol) and triethylamine (11.8 ml, 85 mmol). The mixture was stirred at room temperature for 16 hrs. and taken up in ether (500 ml). The ethereal solution was washed with 1 N hydrochloric acid (1 x 100 ml), water (2 x 50 ml) and brine (1 x 50 ml). After the solution was dried (anhyd. $MgSO_4$) and evaporated, the residue was flash chromatographed on SiO_2-gel column. Elution with 15% ethyl acetate in hexane afforded 4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-2-one (18.4 gm, 99%)as an oil which solidified on standing.

^1H NMR ($CDCl_3$) δ 7.37-7.29 (5H, m), 4.51(1H, dd, J = 6, 3 Hz), 3.5 (1H, dd, J = 16, 6 Hz), 2.93 (1H, dd, J = 16, 3 Hz), 0.9 (3H, s), 0.89 (9H, s), 0.19 (3H, s).

B. 3-(3'-Chloropropyl)-4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-2-one

To a stirred solution of 4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-2-one (9.75 gm, 37 mmoles) in THF (100 ml) at -50°C, a freshly prepared solution of lithium diethylamide (1M in THF, 44 ml, 45 mmole) was added rapidly under nitrogen. The reaction mixture was stirred further for 15 min. at -50°C and then a solution of 1-bromo-3-chloropropane (7.4 ml, 75 mmole) in THF (20 ml) was added. The resulting mixture was stirred for 15 min. at -50°C, after which ammonium chloride (saturated aqueous solution) was added. After the mixture was taken up in ether (2 x 300 ml), it was washed with saturated aqueous sodium chloride. The ether solution was dried ($MgSO_4$) and concentrated, and the residue (17.0 gm) was chromatographed on a SiO_2-gel column. Elution with 5% ethylacetate in hexane afforded 3-(3'-chloropropyl)-4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-1-one as an oil (7.6 gms, 58%).

^1H NMR ($CDCl_3$) δ 7.2-7.4 (1H, m), 4.18 (1H, d, J = 2.5 Hz), 3.5 (2H, t, J = 5 Hz), 3.04 (1H, dt, J = 2.5, 7.5 Hz), 1.7-2.05 (4H, m), 0.9 (9H, s), 0.2 (3H, s).

C. Cis-Methyl-2-phenylpiperidine-3-carboxylate

3-(3'-Chloropropyl)-4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-2-one (3.07 gm, 9.0 mmole) was dissolved in 10% methanolic sulfuric acid and refluxed for 16 hours. At the end of this period, the reaction mixture was cooled, the sulfuric acid was neutralized with sodium bicarbonate and the mixture was taken up in ether (2 x 200 ml). The ethereal solution was washed with water (2 x 50 ml) and dried (anhyd. $MgSO_4$). Evaporation afforded essentially pure 5-chloro-2-carbomethoxy-1-phenylpent-1-ylamine as oil (2.11 gms). The 5-chloro-2-carbomethoxy-1-phenylpent-1-ylamine thus obtained was

dissolved in the DMF (20 ml) and sodium iodide (2.11 gm) and sodium bicarbonate (2.11 gm) were added. The resulting mixture was refluxed for 15 min. At the end of this period, the reaction mixture was cooled and taken up in ether (200 ml). The ethereal solution was washed with water (2 x 50 ml) and dried (anhyd. $MgSO_4$). Evaporation of the ether afforded chromatographically pure cis-methyl 2-phenylpiperidine-3-carboxylate as an oil (1.54 gm, 78%).

^1H NMR ($CDCl_3$) δ 7.31-7.5 (5H, m), 3.95 (1H, d, J = 3.5 Hz), 3.42 (3H, s), 3.39-3.30 (1H, m), 3.01-2.93 (1H, m), 2.84-2.74 (1H, m), 2.22-2.11 (1H, m), 1.90-1.66 (3H, m), 1.53-1.46 (1H, m).

D. Cis-methyl 2-phenylpiperidine-1-(benzyloxycarbonyl)-3-carboxylate

Cis-methyl-2-phenylpiperidine-3-carboxylate (1.54 gm, 7.0 mmole), triethylamine (1.5 ml, 11.0 mmole) and benzyl chloroformate (1.5 ml, 11.0 mmole) were mixed in methylene chloride (45 ml) at 25°C and stirred for 15 hours. At the end of this period, the reaction mixture was taken up in ether (100 ml), washed with water (2 x 50 ml) and dried (anhyd. $MgSO_4$). The solvent was removed under reduced pressure to afford a residue which was chromatographed on a flash SiO_2-gel column. Elution with 1:1 ethyl acetate/hexane afforded cis-methyl 2-phenyl-piperidine-1-(benzyloxycarbonyl)-3-carboyxlate as an oil (1.91 gm, 77%).

^1H NMR ($CDCl_3$) δ 7.34-7.12 (10H, m), 5.97 (1H, bd), 5.30-5.1 (1H, m), 5.17 (1H, s), 4.15-3.90 (1H, m), 3.59 (3H, s), 2.98-2.91 (1H, m), 2.75 (1H, bt, J = 12 Hz), 2.14-2.00 (2H, m), 1.85-1.48 (2H, m).

^{13}C NMR ($CDCl_3$) δ 172.9, 138.3, 126.7, 128.5, 128.0, 127.9, 127.3. 67.4, 54.6, 51.8, 39.7, 25.1, 21.5.

E. Cis-2-phenylpiperidine-1-(benzyloxycarbonyl)-3-carboxamide

To a suspension of ammonium chloride (1.66 gm, 31 mmole) in benzene (60 ml) at -5°C, was slowly added a 2M solution (15.6 ml, 31 mmole) of trimethyl aluminum in hexane. After addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 1 hr until gas evolution had ceased. A solution of cis-methyl 2-phenylpiperidine-1-(benzyloxycarbonyl)-3-carboxylate (2.2 gm, 6.2 mmole) in benzene (10 ml) was added and the solution was maintained at 50°C for 16 hours. The reaction mixture was cooled to room temperature and was carefully quenched with 5% HCl. The resulting mixture was filtered through diatomaceous earth (Celite (trademark)) and the residue was washed with methylene chloride (200 ml). The organic layer was separated while the aqueous layer was made basic and extracted with methylene chloride (200 ml). The organic extracts were combined, dried (anhyd. $Mg(SO_4)$) and concentrated in vacuo to afford a residue which was suspended in 1:1 ether-pentane to afford cis-2-phenylpiperidine-1-(benzyloxycarbonyl)-3-carboxamide as a white solid (1.4 gm, 66%). M.p. 171°C.

^1H NMR ($CDCl_3$) δ 7.35-7.28 (10H, m), 5.86 (1H, d, J = 4.9 Hz), 5.66-5.58 (1H, m), 5.48-5.37 (1H, m), 5.21 (1H, d, J = 12 Hz), 5.13 (1H, d, J = 12 Hz), 4.02 (1H, bd, J = 13 Hz), 2.9-2.74 (2H, m), 2.11-1.98 (2H, m), 1.86-1.76 (1H, m), 1.66-1.5 (1H, m).

HRMS Calc'd for $C_{20}H_{22}N_2O_3$: 338,1630. Found: 338.1634.

F. Cis-1-(benzyloxycarbonyl)-3-amino-2-phenylpiperidine

Cis-2-phenylpiperidine-1-(benzyloxycarbonyl)-3-carboxamide (1.4 gm, 4.1 mmole) was dissoved in dry tert.-butanol (40 ml) at 50°C, and lead tetraacetate (1.9 gm, 4.3

mmole) was added. The resulting brown reaction mixture was refluxed for 0.5 hours. Additional lead tetraacetate (1.9 gm, 4.3 mmole) was added over a period of 1 hour. At the end of this period, the reaction mixture was poured into cold 1N hydrochloric acid and filtered through diatomaceous earth (Celite (trademark)). The aqueous phase was extracted with ethyl acetate (3 x 100 ml) and the combined organic layers were washed successively with water, 5% aqueous sodium hydroxide, water, and brine and dried (anhy. $MgSO_4$). Evaporation of the solvent under reduced pressure afforded a residue which was chromatographed on a SiO_2-gel column. Elution with 25% ethyl acetate in hexane afforded chromatographically homogeneous cis-1-(benzoyloxycarbonyl)-3-(N-tert-butoxycarbonyl)-2-phenylpiperidine (1.1 gm) as oil. This was dissovled in ethyl acetate (20 ml) and hydrogen chloride gas was bubbled through it for 5 min. Then the reaction mixture was taken up in aqueous ammonia and extracted with methylene chloride (2 x 200 ml). The organic extracts were combined, dried and evaporated to afford chromatographycally pure cis-1-(benzyloxycarbonyl)-3-amino-2-phenylpiperidine as oil (0.830 gms, 65%).

Cis-1-(benzoyloxycarbonyl)-3-(N-tert.-butoxycarbonyl)-2-phenylpiperidine: ^1H NMR ($CDCl_3$) δ 7.39-7.16 (10H, m), 5.46 (1H, bd, J = 6 Hz), 5.13 (1H, d, J = 13 Hz), 4.98 (1H, d, J = 13 Hz), 4.14-3.93 (2H, m), 3.23 (1H, bt), 1.9-1.5 (5H, m), 1.39 (9H, s).

Cis-1-(benzyloxycarbonyl)-3-amino-2-phenylpiperidine: ^1H NMR ($CDCl_3$) δ 7.42-7.36 (2H, m), 7.32-7.12 (8H, m), 5.26 (1H, d, J = 5 Hz), 5.07 (1H, d, J = 12 Hz), 4.95 (1H, d, J = 12 Hz), 4.06 (1H, bd, J = 12, 5 Hz), 3.12-3.08 (2H, m), 1.88-1.53 (4H, m).

G. Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine

Cis-1-(benzyloxycarbonyl)-3-amino-2-phenylpiperidine (0.78 gm, 2.5 mmole) was dissolved in methanol (25 ml) and the pH of the medium was adjusted to 5 with the help of methanolic hydrochloric acid. To it crushed molecular sieves (1.0 gm), sodium cyanoborohydride (0.163 gm, 2.5 mmole) and o-methoxybenzaldehyde (0.411 gm, 3.0 mmole) were added, and the resulting reaction mixture was stirred at room temperature for 16 hours. At the end of this period, the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate was taken up in aqueous ammonium hydroxide. The aqueous phase was extracted with methylene chloride (3 x 60 ml) and dried (anhyd. $MgSO_4$). The solvents were removed under reduced pressure to afford an oily residue (1.18 gm). This was dissolved in ethanol (27 ml) and 10% palladium on carbon (1.2 gm) and ammonium formate (0.864 gm, 14 mmole) were added. The resulting reaction mixture was stirred at 25°C for 16 hrs. At the end of this period, the reaction mixture was filtered through diatomaceous earth (Celite (trademark)), which was washed with ethanol (50 ml) and methylene chloride (100 ml). The solvents were removed under vacuum to afford a solid which was taken up in aqueous ammonium hydroxide and extracted with methylene chloride (3 x 60 ml). The organic extracts were combined and dried (anhyd. $MgSO_4$). Evaporation of the solvents under pressure afforded a yellow oil from which cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (728 mg, 83%) was isolated as white solid by treatment with ether-HCl. This was crystallized from ethanol/methanol to afford the hydrochloride salt of the title compound (0.58 mg, m.p. 250°C).

EXAMPLE 64

(+) S,S-Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine

The title compound was prepared according to the

procedure of Example 63, starting with enantiomerically pure (+)R-4-phenylazetidin-2-one.

M.p. 249°C (dec., HCl salt). $[\alpha]_D$ = +77°) (c=1, MeOH).

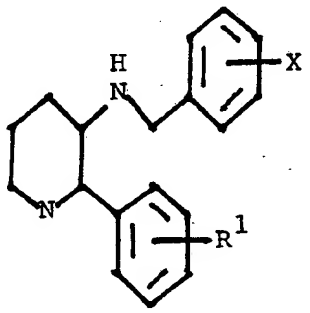
EXAMPLE 65

(-)R,R-Cis-3-(2-methoxyphenylamin)-2-phenylpiperidine

The title compound was prepared by the procedure described in Example 63, starting with enantiomerically pure (-)S-4-phenylazetidin-2-one.

M.p. 251°C (dec., HCl salt). $[\alpha]_D$ = -7.9° (c = 1, MeOH).

The title compounds of examples 66-70 have the following general formula and were prepared by a procedure simlar to that described in Example 1.



EXAMPLE 66

Trans-3-(2-chlorobenzylamino)-2-phenylpiperidine (R_1=H, X=2-Cl). M.p. > 255°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.42-7.02 (9H, m), 3.69 (1H, d, J = 13.9 Hz), 3.56 (1H, d, J = 13.8 Hz), 3.80 (1H, d, J = 9.1 Hz), 3.09 (1H, bd, J = 11.4 Hz), 2.75 (1H, dt, J = 11.8, 2.9 Hz), 2.62-2.54 (1H, m), 2.29-2.23 (1H, m), 1.79-2.23 (2H, m), 1.34-1.24 (1H, m). HRMS Calc'd for $C_{18}H_{21}N_2Cl$: 300.1392. Found: 300.1387.

EXAMPLE 67

Cis-3-benzylamino-2-(3-trifluorophenyl)-piperidine (R_1=3-CF_3, X = H). M.p. > 270°C (dec., HCl salt). ^{1}H

NMR (HCl salt, MeOH-$CDCl_3$) δ 8.85 (2H, bs), 8.74-8.44 (2H, m), 8.21 (1H, 2), 8.16-8.02 (4H, m), 5.97 (1H, bs), 4.86 (1H, bs), 4.58 (1H, t, J = 10 Hz), 4.46-4.36 (2H, m), 4.2-4.14 (2H, m), 3.24-3.08 (3H, m), 2.75 (1H, bd, J = 10 Hz). HRMS Calc'd for $C_{19}H_{21}N_2CF_3$: 296.1889. Found: 296.1904.

EXAMPLE 68

Cis-3-benzylamino-2-phenylpiperidine (R^1 = H, X = H). M.p. 264°C (dec. HCl salt). ^{1}H-NMR (CDCl) δ 6.8-7.4 (1H, M); 3.63 (1H, d, J = 13 Hz); 3.42 (1H, d, J = 13 Hz); 3.38 (1H, d, J = 7 Hz); 3.02 (1H, bt); 2.58-2.8 (2H, m); 2.2 (1H, m); 1.5-1.8 (3H, m); 1.2-1.38 (2H, m). HRMS (Calcd. for $C_{10}H_{22}N_2$: 266.1783. Found 266.1764.

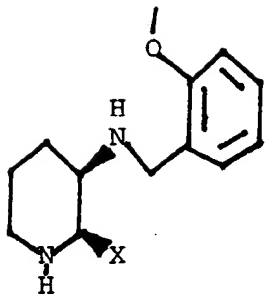
EXAMPLE 69

Trans-3-(2-methoxybenzylamino)-2-phenylpiperidine (R_1 = H, X = 2-OMe). M.p. > 250°C (dec., HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.29-7.24 (5H, m), 7.14 (1H, t, J = 8 Hz), 6.97 (1H, d, J = 8 Hz), 6.81 (1H, t, J = 8 Hz), 6.67 (1H, d, J = 8 Hz), 3.68 (1H, d, J = 14 Hz), 3.47 (1H, d, J = 14 Hz), 3.39 (3H, s), 3.38-3.34 (1H, m), 3.06 (1H, bd, J = 14 Hz), 2.73 (1H, td, J = 9, 3 Hz), 2.51 (1H, td, J = 8, 3 Hz), 2.32-2.2 (1H, m), 1.76-1.5 (2H, m), 1.36-1.2 (1H, m). MS (M^+298.18).

EXAMPLE 70

Cis-3-benzylamino-2-(4-phenylphenyl)piperidine (R_1=4-Ph, X = H) M.p. 268°C (HCl salt). ^{1}H NMR (CD_3OH, HCl salt) δ 7.8 (4H, m), 7.59 (2H, d, J = 5 Hz), 7.40 (2H, t, J = 3 Hz), 7.38=7.24 (6H, m), 4.98 (1H, bs), 3.98 (1H, bs), 3.87 (1H, d, J = 10 Hz), 3.68-3.58 (2H, m), 3.34-3.22 (3H, m), 2.46-2.16 (3H, m), 2.01-1.90 (1H, m). HRMS Calc'd for $C_{24}H_{26}N_2$: 342.2096. Found: 342.2057.

The title compounds of Examples 71-75 have the following general formula and were prepared by a procedure similar to that described in Example 1.



EXAMPLE 71

Cis-3-(2-methoxybenzylamino)-2-(3-thienyl)-piperidine (X=3-thienyl). M.p. 239°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.25-7.11 (3H, m), 7.03 (1H, dd, J = 7.3, 1.7 Hz), 6.85-6.82 (2H, m), 6.73 (1H, d, J = 8.2 Hz), 3.94 (1H, bs), 3.73 (1H, d, J = 13.7 Hz), 3.57 (3H, s), 3.45 (1H, d, J = 13.7 Hz), 3.20 (1H, bd, J = 10.4 Hz), 2.82 (1H, d, J = 2.7 Hz), 2.76 (1H, dt, J = 12.5, 3.1 Hz), 2.11 (1H, bd, J = 13.4 Hz), 1.97-1.84 (1H,m), 1.57 (1H, tt, J = 13.4, 3.5 Hz), 1.36 (1H, bd, J = 13.2 Hz). HRMS Calc'd for $C_{17}H_{22}N_2OS$: 302.1535. Found: 302.1444.

EXAMPLE 72

Cis-3-(2-methoxybenzylamino)-2-benzylpiperidine (X=benzyl). M.p. 241°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, dd, J = 7.3, 1.6 Hz), 7.29-7.2 (6H, m), 6.93 (1H, dt, J = 7.4, 1.0 Hz), 6.88 (1H, dd, J = 8.2, 0.7 Hz), 3.89 (1H, d, J = 13.5 Hz), 3.85 (1H, s), 3.70 (1H, d, J = 13.5 Hz), 3.00-2.89 (2H, m), 2.82 (1H, s), 2.79 (1H, d, J = 3.6 Hz), 2.71-2.67 (1H, m), 2.57 (1H, dt, J = 10.7, 3.2 Hz), 1.97-1.92 (1H, m), 1.75-1.63 (1H, m), 1.44-1.36 (2H, m). HRMS Calc'd for $C_{20}H_{26}N_2O$: 310.2045. Found: 310.2073.

EXAMPLE 73

Cis-3-(2-methoxybenzylamino)-2-cyclohexylpiperidine (X=cyclohexyl). M.p. 225°C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.13-7.31 (2H, m), 6.9 (1H, t, J = 8 Hz), 6.82 (1H, d, J = 9 Hz), 3.9 (1H, d, J = 14 Hz), 3.81 (3H, s), 3.6 (1H, d, J = 15 Hz), 3.11 (1H, bd, J = 9 Hz), 2.72 (1H, bs),

2.6 (1H, t, J = 10 Hz), 2.19 (1H, d, J = 9 Hz), 2.11 (1H, bd, J = 12 Hz), 2.01-1.53 (1H, m), 1.38-1.04 (6H, m), 0.92-0.65 (2H, m). HRMS Calcd for $C_{19}H_{30}N_2O$: 302.2358. Found: 302.2352.

EXAMPLE 74

Cis-3-(2-methoxybenzylamino)-2-tert.butylpiperidine (X=tert. butyl). Mp. 251°C (HCl salt). ^{1}H NMR ($CDCl_3$)δ 7.33 (1H, dd, J = 7.3, 1.6 Hz), 7.21 (1H, dd, J = 7.8, 1.7 Hz), 6.90 (1H, dt, J = 7.4, 0.95 Hz), 6.84 (1H, d, J = 8.2 Hz), 3.91 (1H, d, J = 13.6 Hz), 3.81 (3H, s), 3.55 (1H, d, J = 13.6 Hz), 3.13 (1H, bd, J = 12.1 Hz), 2.88 (1H, bs), 2.61 (1H, dt, J = 12.3, 2.9 Hz), 2.19 (1H, d, J = 1.9 Hz), 2.12 (1H, bd, J = 12.9 Hz), 1.76-1.66 (1H, m), 1.35-1.22 (2H, m), 9.95 (9H, s). HRMS Calc'd for $C_{17}H_{28}N_2O$: 276.2201. Found: 276.2217.

EXAMPLE 75

Cis-3-(2-methoxybenzylamino)-2-(3-furanyl)-piperidine (X = 3-furanyl). M.p. 247°C (HCl salt). ^{1}H NMR ($CDCl_3$)δ 7.34 (2H, d, J = 1.4 Hz), 7.19 (1H, dt, J = 7.7, 1.7 Hz), 7.11 (1H, dd, J = 7.3 1.6 Hz), 6.85 (1H, t, J = 7.4 Hz), 6.77 (1H, d, J = 8.1 Hz), 6.15 (1H, td, J = 1.2 Hz), 3.8 (2H, d, J = 14.0 Hz), 3.65 (3H, s), 3.54 (1H, d, J = 13.6 Hz), 3.14 (1H, bd, J = 12.7 Hz), 2.75 (2H, dt, J = 12.1, 3.2 Hz), 2.09 (1H, bd, J = 13.6 Hz), 1.93-1.83 (1H, m), 1.54 (1H, tt, J = 13.2, 3.5 Hz), 1.36 (1H, bd, J = 13.1 Hz). HRMS Calc'd for $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1682.

EXAMPLE 76

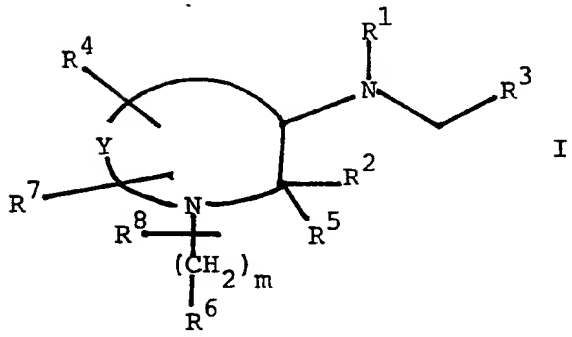
Cis-3-(2-methoxybenzylamino)-2-phenylazacycloheptane

The title compound was prepared according to the procedure of Example 63 starting with (±)-4-phenyl-azetidine-2-one and using 1-bromo-4-chlorobutane in procedure B instead of 1-bromo-3-chloropropane. M.p. 230-230°C (dec HCl salt). ^{1}H-NMR ($CDCl_3$) δ 1.21 (m, 1H) 1.55 (m, 1H), 1.80 (m, 5H), 2.75 (m, 1H), 3.06 (m, 1H),

3.36 (m, 1H), 3.39 (s, 1H), 3.45 (d, 1H, J = 13 Hz), 3.50 (m, 1H), 6.62 (d, 1H, J = 6Hz), 6.76 (t, 1H, J = 6 Hz), 6.91 (d, 1H, J = 6 Hz), 7.12 (m, 2H), 7.22 (m, 4H). HRMS Calc'd. for $C_{20}H_{27}N_2O$: 311.2124. Found: 311.2132.

CLAIMS

1. A compound of the formula



I

wherein Y is $(CH_2)_n$ wherein n is an integer from 2 to 4, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7;

m is an integer from 0 to 6, and any one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

R^1 is (C_1-C_6) alkyl or hydrogen;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight of branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl

and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6) alkylamino, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl;

R^5 is hydrogen;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6) alkylamino, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and

R^4, R^6, R^7 and R^8 are each independently selected from hydrogen hydroxy, halo, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^2, with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4, R^6 nor R^7 can form, together with the carbon to which it is attached, a ring with R^5, and (c) when R^4 and R^7 are attached to the same carbon atom, then either each of R^4 and R^7 is independently selected from hydrogen and (C_1-C_6) alkyl, or R^4 and R^7, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached;

and the pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen; R^2 is phenyl, 2-fluorophenyl, 3-fluorophenyl or 3-methoxyphenyl; R^3 is 2-methoxyphenyl; R^4, R^5, R^6 and R^7 are hydrogen; n is 3 or 4; and m is 0.

3. A compound according to claim 1, wherein said compound is cis-3-(2-chlorobenzylamino)-2-phenylpiperidine;

4. A compound according to claim 1, wherein said compound is cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine.

5. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine.

6. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(2-chlorophenyl)-piperidine.

7. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(2-methylphenyl)-piperidine.

8. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(3-methoxyphenyl)-piperidine.

9. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(3-fluorophenyl)-piperidine.

10. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(3-chlorophenyl)-piperidine.

11. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-phenylpiperidine.

12. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(3-methylphenyl)-piperidine.

13. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(4-fluorophenyl)-piperidine.

14. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-phenylazacycloheptane.

15. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-(3-thienyl)-piperidine.

16. A compound according to claim 1, wherein said compound is 3-(2-methoxybenzylamino)-4-methyl-2-phenylpiperidine.

17. A compound according to claim 1, wherein said compound is 3-(2-methoxybenzylamino)-5-methyl-2-phenyl-piperidine.

18. A compound according to claim 1, wherein said compound is 3-(2-methoxybenzylamino)-6-methyl-2-phenyl-piperidine.

19. A compound according to claim 1, wherein said compound is 3-(2-methoxybenzylamino)-2,4-diphenyl-piperidine.

20. A compound according to claim 1, wherein said compound is cis-3-(2-methoxybenzylamino)-2-phenyl-pyrrolidine.

21. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of anxiety, colitis, migraine, psychosis, pain, inflammatory diseases such as arthritis, psoriasis, asthma and inflammatory bowel disease , and rheumatic diseases such as fibrositis in a mammal, comprising an amount of a compound according to claim 1 effective in preventing or alleviating such condition, and a pharmaceutically acceptable carrier.

22. A method of treating or preventing a condition selected from the group consisting of anxiety, colitis, migraine, psychosis, pain and inflammatory diseases such as arthritis, psoriasis, asthma and inflammatory bowel disease, and rheumatic diseases such as fibrositis in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or alleviating such condition.

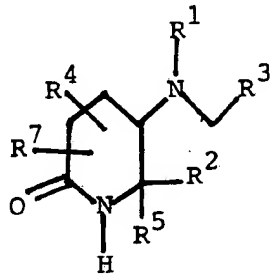
23. A pharmaceutical composition for antagonizing the effects of substance P in a mammal, comprising a substance P antagonizing effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier.

24. A method of antagonizing the effects of substance P in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

25. A pharmaceutical composition for treating or preventing a disorder in a mammal resulting from an excess of substance P, comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

26. A method for treating or preventing a disorder in a mammal resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing effective amount of a compound accoriding to claim 1.

27. A compound of the formula



I'

wherein R^1, R^2, R^3, R^4, and R^5 are as defined in claim 1.

28. A radioactive isotope of a compound according to claim 1, said radioactive isotope being selected from the group consisting of the tritium and ^{14}C-isotopes of said compound.

29. A radioactive isotope as claimed in claim 28, wherein said radioactive isotope is a tritium or ^{14}C-isotope of a compound according to any one of claims 1-20.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/00116

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 211/56; A61K 31/445

U.S.CL. 546/223; 514/317

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
U.S.CL:	546/223; 514/317

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

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III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A, 2,838,516 (HOFFMAN ET AL.) 10 JUNE 1958. See entire document.	1-13,15-19
A	US,A, 3,458,521 (ALEXANDER ET AL.) 29 JULY 1969.	1-13,16-19

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 MAY 1990	04SEP 1990

International Searching Authority	Signature of Authorized Officer
ISA/US	ALAN L. ROTMAN

Form PCT/ISA/210 (second sheet) (Rev.11-87)